Title page

The effects of acute inflammation on cognitive functioning and emotional processing in humans: a systematic review of experimental studies.

Short title: Inflammation, cognition and emotional processing

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Abstract

Objective: The cognitive neuropsychological model of depression proposes that negative biases in the processing of emotionally salient information ~~may~~ have a central role in the development and maintenance of depression. We ~~have~~ have conducted a systematic review to determine whether acute ~~inflammation~~experimental inflammation is associated with changes to cognitive ~~functioning~~ and emotional processing that are thought to cause and maintain depression.

Methods: We identified ~~controlled,~~ experimental studies in which healthy individuals were administered an acute inflammatory challenge (bacterial endotoxin / vaccination) and standardised tests of cognitive function were performed.

Results: Fourteen ~~relevant~~ references were identified, reporting findings from 12 independent studies on 345 ~~individual healthy~~ participants. Methodological quality was rated strong or moderate for 11 ~~of the 12~~ studies. ~~Inflammation~~Acute experimental inflammation was triggered using a variety of agents (including endotoxin from E.Coli, S.Typhi, S.Abortus Equi and Hepatitis B vaccine) and cognition was assessed over hours to months, using cognitive tests ~~that covered the domains~~ of i) attention / executive functioning, ii) memory and iii) social / emotional processing. Studies found mixed evidence that acute ~~inflammation~~experimental inflammation caused changes to attention / executive functioning (2 of 6 studies showed improvements in attention executive function compared to control), changes in memory (3 of 5 studies; improved reaction time: reduced memory for object proximity: poorer immediate and delayed memory) and changes to social / emotional processing (4 of 5 studies; ~~), including findings that inflammation~~ reduced ~~ability to perceive~~perception of emotions ~~from photographs~~, increased avoidance of punishment / loss experiences, and increased ~~feelings of~~ social disconnectedness).

Conclusions: ~~Though preliminary, findings are consistent with the hypothesis that inflammation~~Acute experimental inflammation causes negative biases in social and emotional processing that could explain observed associations between inflammation and depression~~causes depression, at least in part, via effects on social / emotional neurocognitive processing~~.

Text

Introduction

Previous research has indicated that inflammation may contribute to the development of depression. Cross-sectional and longitudinal observational studies have shown that depression is associated with increases in markers of inflammation (c-reactive protein, IL-1, IL-6)[1-3]. Controlled, experimental studies among depression-free individuals have shown that acute ~~inflammation~~experimental inflammation, triggered by the administration of an endotoxin or attenuated vaccine, provoked short term increases in depressive symptoms, which correlated with the increases in inflammatory markers, particularly IL-1 receptor antagonist (IL-1Ra), IL-6 and tumour necrosis factor alpha (TNF-α)[4,5]. Alterations in functioning of central monoamines pathways (serotoninergic, glutamatergic and dopaminergic) that are associated with inflammation are likely be important [6-8], though the exact mechanisms by which inflammation might cause depression have not been fully elucidated.

Recently, there has been growing interest in a cognitive neuropsychological model of depression (see figure 1)[9,10]. This proposes that negative biases in the cognitive processing of emotionally salient information have a central role in the development and maintenance of depressed mood. In this model, genetic and environmental factors negatively influence this emotional processing indirectly via effects on monoamine pathways. Negative biases in emotional processing in turn result in the development of negative cognitive schemata, which contribute to the development and maintenance of depressed (i.e. low) mood. The state of clinical depression, characterised by anhedonia and dysphoria, is considered to be a learnt state that develops over time in response to repeated negative experiences.

The evidence supporting this neurocognitive model of depression is substantial. Negative biases in domains of emotional perception[11,12], emotional attention[13], emotional memory[9,14] and processing of information relating to performance feedback, reward and punishment[15], have been shown among people with depression and among those at increased risk of depression[10]. Such biases in

information processing can be provoked by impairing central serotonergic functioning, e.g in response to tryptophan depletion[16,17] and are reduced following exposure to antidepressants[9,18-22] and some psychological treatments[23-25]. Experimental studies have shown that inflammation can result in alterations in neurological and behavioural responses to reward, which are consistent with the cognitive neuropsychological model of depression, though the findings of such studies have been mixed[26,27].

Currently, it is not clear whether acute inflammation causes short-term changes to cognitive functioning or the negative biases in emotional processing that are thought to cause and maintain depression. We have conducted a systematic review to clarify the short-term effects of acute experimental inflammation in human subjects on:

1. cognitive functioning,
2. ~~social /emotional~~the processing of emotionally and socially salient information (henceforth social / emotional processing)~~.~~

Methods and materials

The reporting of this review complies with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[28].

Inclusion criteria

We identified studies designed to establish the effects of ~~acute inflammation~~acute experimental inflammation on cognitive processing in healthy humans.

Population

We included studies of healthy adult participants (>18 years of age) only, to exclude any confounding or moderating~~ulating~~ influences of co-existing physical health conditions (and their treatments) on the association between acute inflammatory response and changes in cognition.

Intervention

Studies were required to induce acute inflammation among a proportion of their study participants by the administration of an inflammatory stimulant, such as an endotoxin or a vaccine.

Comparators

Eligible studies were required to include a comparison group composed of participants undergoing identical assessments under similar conditions. We accepted studies that did and did not include the delivery of a placebo intervention in place of the endotoxin /vaccine.

Outcomes

The main outcomes of interest were the comparisons of performance on cognitive testing between the intervention and the control groups. Eligible studies were required to include standardized measures of cognitive functioning, applied to intervention and control groups under the same conditions, at similar times relative to the administration of the intervention / control and to report cognitive findings in a way that enabled direct comparison between groups. We did not limit studies by the number or types of cognitive domains tested. The findings from the wide range of cognitive tests were grouped into major domains of i) attention / executive functioning, ii) memory and iii) social / emotional processing, by consensus within our group, based on the description of the test and its delivery in the study report and with reference to the wider academic literature on neurocognitive functioning.

Study design

Since cognitive testing can be influenced by environmental factors, the study set-up and practice effects, only controlled studies, either simple parallel group or cross-over design, were eligible for inclusion. We did not limit studies to those that randomly allocated subjects to the intervention versus control, or that maintained blinding of intervention allocation among subjects and / or outcome assessors, though we considered these details of study design when assessing study quality and interpreting findings.

Other limiters

We did not limit studies included by date or language of publication.

Electronic search strategies were designed by the study team using exploded keyword search terms and free text terms relating to main concepts, namely 1) inflammation and inflammatory mediators and 2) cognition and neuropsychological testing. The initial search was designed for Medline (see online appendix) and adaptations were made for other databases, as appropriate, to accommodate differences in database keywords. Electronic database searches were conducted on the 5th January 2015 and updated on the 4th January 2016. The databases searched included MEDLINE (1946-onwards), EMBASE (1974-onwards), and PsycINFO (1806-onwards) using the Ovid database interface. Forward and backward citation searches of eligible studies were conducted in August 2015 and updated in Sept 2016, to identify further eligible papers and authors were contacted where a full text version of the paper could not be acquired. ~~Details of electronic search strategies used are included in the online appendix.~~

Data were double-extracted by 2 independent researchers using standardised data extraction sheets. Methodological quality was assessed by two independent reviewers (JB, LT) using the Quality Assessment Tool for Quantitative Studies by the Effective Public Health Practice Project (EPHPP), which has been widely used in systematic reviews to assess quality of quantitative studies, including studies using experimental design[29]. This assessment tool was comprised of sections relating to selection bias, study design, control for confounding variables, blinding of allocation, data collection methods and accounting for withdrawals and dropouts. Section scores were combined into a global rating score, as described the by developers of the assessment. The intervention integrity and appropriateness of statistical analysis were also rated in the EPHPP, but did not contribute to the global score.

Due to the variability in neurocognitive tests conducted and cognitive domains assessed, we did not conduct a quantitative synthesis (meta analysis) of results. Findings of independent studies are presented in tables and synthesised narratively, using a vote-count method where findings are mixed and taking consideration of differences in experimental design and methodological quality.

Where findings from single independent studies had been published or presented in multiple study reports, such reports ~~are~~ were combined to avoid double counting studies.

Results

The electronic search produced 3623 citations of potential interest, from which seven eligible papers were identified. Forward and backwards citation searching resulted in identification of a further seven eligible papers (see Figure ~~1~~2). In two instances findings from single independent studies were reported in two separate papers; Cohen et al[30] used a subset of 10 participants included in the study by Reichenberg[4]: Eisenberger and colleagues presented related findings from the same experiment in 2 separate papers [31,32]. Consequently, we present findings of 14 separate reports from 12 independent studies[4,27,30-41].

The 12 independent studies recruited 351 individual participants. Six subjects were subsequently excluded from analyses[39], so results are presented for the total population of 345. In nine studies healthy male subjects only were recruited; three studies recruited mixed-sex populations. The mean age of subjects studied was 24.1 years.

Four studies used randomized, double-blind, placebo controlled design, 7 used randomized double blind, placebo controlled cross-over design and 1 used non-randomized controlled design. The methods used to induce ~~inflammation~~experimental inflammation within the participants were injections of: *E. coli* endotoxin in 7 studies (0.2 – 0.8 ng /kg) , *Salmonella typhi* endotoxin in *3* studies (0.025mg) , *Salmonella abortus equi* endotoxin in 1 study (0.8ng / kg) and Hepatitis B triple vaccine in one study (3 doses of 20 micrograms of recombinant Hepatitis B surface antigen) . See table 1 for description of the main methodological characteristics of included studies.

Inflammatory response was measured in studies by assaying combinations of pro-inflammatory and anti-inflammatory cytokines, and antibodies to Hepatitis B mediators. All 12 studies measured IL-6, 11 studies measured TNF-a, 7 studies measured IL-1ra and 4 studies measured IL-10. One study assayed soluble TNF-Receptor, another TNF-Rp55 and another assayed antibodies against

Hepatitis B. Studies used repeated assays of cytokines / antibodies, between 0.5 hours to 25 weeks, though most performed assays between 1 and 6 hours following endotoxin administration.

Of the 12 studies conducted, 11 provided comparison of cytokine levels in the endotoxin / vaccine group compared to placebo; 1 study[41] compared post endotoxin level in the endotoxin group with baseline levels (i.e. pre-endotoxin). Eleven studies confirmed significant increases in levels in at least some of the cytokines measured following injection with endotoxin; Of note, Brydon et al did not detect increases in TNF-a or IL-1Ra[33], and Harrison et al did not detect an increase in TNF-a[36]; both studies used S.Typhi (0.025mg) and assayed for TNF-a at 3 and 4 hours, respectively. One study reported an increase in antibodies against Hepatitis B following Hepatitis B vaccination, but no associated increase in serum cytokines measured[40].

Assessment of cognition

Studies reported findings from a broad range of specific tests of neurocognitive functioning covering the domains of attention and executive function (6 studies), memory (5 independent studies) and social / emotional processing (5 studies). Details of the specific tests used in each of the 12 studies are presented in the online appendix. Studies conducted repeated assessments of cognitive functioning between 1 hour and 25 weeks following endotoxin / vaccination, though with most studies focussing on the period 1 – 9 hours following endotoxin administration.

Of the 12 studies in people who had received endotoxin or vaccines, 7 independent studies (reported in 9 papers [4,27,30-32,34,36,39,40]) showed some change in cognitive functioning across the domains tested. Of the 7, 4 showed some impairment in cognitive functioning in people receiving endotoxin / vaccine compared to controls (memory for object location, re-orientation of response to reward versus punishment, emotional recognition in others and feelings of social disconnectedness)[27,31,32,36,39], 1 showed improvement in cognitive functioning (reduced Stroop reaction time)[40], and 2 showed mixed results, with improvement in some domains (~~improvements in~~ attention, executive functioning and working memory), and impairment in others (immediate and

delayed verbal and non-verbal memory, social / emotional processing)[30,34]. The effects of inflammatory challenges on cognition from studies included are presented in Table 2.

Among studies showing some effects of their intervention on neurocognitive functioning, from the information reported, there was no clear association between the study design and the observed effects (e.g. proportion of male subjects, parallel versus cross-over design or inflammatory challenge used).

Attention and executive function

Of the 6 studies assessing attention and executive functioning, 2 studies showed some effects of ~~inflammation~~acute experimental inflammation.

One study found significant group x condition interactions (incongruent vs congruent trials) for reaction times and number of errors on the Stroop test[40]. Post hoc tests revealed better performance on the Stroop test in the sample receiving Hepatitis B vaccination. This finding was not replicated in 3 other studies using the Stroop test that reported no difference between the experimental and control groups (time to respond and / or number of errors)[33,35,41]. The differences in these study findings are difficult to interpret and it is not clear whether ~~methodological~~ differences in the way inflammation was induced (i.e. Hep B vaccination versus endotoxin), the magnitude and nature of the consequent inflammatory response or the timing of assessments of cognition (4 days to 25 weeks in the Hep B vaccination study compared to 1.5 to 8 hours in the endotoxin studies) are attributable for differences in findings~~. As a result it is not clear whether these findings indicate that the impact of an acute inflammatory challenge on attention occurs later than most studies assessed cognition,~~ or whether this was a chance finding. Further studies are required.

Cohen et al reported on a subgroup (n=10) of the study by Reichenberg and found improvements in attention and executive functioning using the Digit Span Backwards test ($p = 0.008$). However, Reichenberg et al found no such effects in the larger parent population using a broader range of

other tests of attention and executive functioning, which casts doubt on the significance of the Cohen finding.

Studies comparing performance between experimental and control groups on attention / executive functioning using ~~studies~~ tests other than the Stroop (including digit span forwards, WAIS digit symbol tests, simple reaction tasks, Ruff 2 and 7 number cancellation test, the Continuous Performance Test, the attention subscore from the Wechsler Memory Scale-R, Trail Making Tests or word fluency) found no significant differences. One study using the serial addition task found a non-significant trend for subjects in the experimental group to perform better than controls ($p=0.07$)[41].

Memory

Of the 5 independent studies assessing the impact of ~~inflammation~~acute experimental inflammation on memory, 3 studies reported some mixed changes associated with inflammation.

Grigoleit et al (2011) showed reduced reaction time on the n-back test among subjects taking high dose E. Coli endotoxin compared to placebo, but not in low dose endotoxin compared to placebo ($p<0.01$)[34]. No difference in accuracy of recall was found. Reichenberg et al (2001) showed impairment of immediate and 30 minute delayed verbal memory ($p = 0.01$ and $p=0.03$, respectively), non-verbal memory ($p=0.008$ and $p=0.01$, respectively) and reduced immediate word list recall ($p=0.01$) in the endotoxin group[4]. Harrison et al (2014) showed reduced memory of object location ($p=0.039$), but not object identity ($p=0.43$) or procedural memory ($p=0.33$) amongst those receiving endotoxin[36].

Of the negative studies, one study reported no effects on verbal ($p=0.60$), visual ($p=0.59$) or delayed memory ($p=0.97$)[35]. Krabbe et al found a non-significant trend for people treated with endotoxin to have better immediate recall than those in the control condition (post hoc comparison, $t=-2.0$, $p=0.08$), but no effect on delayed recall or working memory[37].

Emotional and social processing

Five independent studies included measures of processing of emotionally and/or socially relevant information [27,31,32,34,38,39]. Of these, 4 showed some alteration in emotional/ social processing associated with ~~inflammation~~acute experimental inflammation [27,31,32,34,39].

Two studies investigated the effects of endotoxin on subjective experiences of social disconnectedness [32,39]. Both found increased subjective feelings of social disconnectedness following administration of endotoxin versus placebo.

Of the two studies conducting the Reading the Mind in the Eyes (RME) test, Moieni et al found that subjects receiving endotoxin gave significantly fewer correct answers during the RME test (group x time interaction, $p<0.01$)[39]. Kullmann and colleagues found no difference between endotoxin and control groups in behavioural responses to the RME test, though they did report altered neural activity (increased responses in fusiform gyrus, temporo-parietal junction, superior temporal gyrus and precuneus) in the endotoxin group[38]. The authors interpreted these neurological findings as indicating possible compensatory mechanisms or greater social cognitive processing activity, in response to endotoxin. Of note, Moieni et al used double the dose of E.Coli endotoxin compared to Kullmann et al and provoked higher levels of TNF-a (140pg/ml at 2 hours[42] compared to 70pg/ml at 1.75 hours in Kullmann et al) which could account for differences in behavioural responses to the RME task..

Two studies investigated the effects of endotoxin on responses to rewards versus loss. Harrison et al showed that exposure to inflammation resulted in individuals reducing selection of high probability reward and increasing avoidance of high probability loss, which could best be attributed to increased sensitivity to loss [27]. However, Eisenberger et al found no differences with regards to behavioural responses to rewarding vs neutral vs loss experiences[31]. These studies used different inflammatory challenges, with Eisenberger et al demonstrating larger inflammatory response; IL-6 peaked at about 150pg/ml at 3 hours in the Eisenberger study compared to 45.6 pg/ml at 3.5 hours

in the Harrison study*. Differences in findings are therefore unlikely to be attributable to differences in the inflammatory response.

Grigoleit et al randomized subjects to either high dose endotoxin vs saline (n=16) or low dose endotoxin vs saline (n=18) using a double blind cross-over study, and investigated individuals' ability to recall emotional and neutral faces over 24 hours following injection[34]. Subjects receiving low dose endotoxin 24 hours previously demonstrated reduced ability to recall emotional faces compared to individuals receiving saline, whereas ability to recall neutral faces remained unaffected. Subjects receiving high dose endotoxin 24 hours previously demonstrated no effects on recall.

Study Quality

Findings from the assessments of study quality are presented in Table 3. Of the 12 independent studies assessed using the global rating of quality, 2 were rated as strong (i.e. no weak domains), 9 were rated as being moderate (1 weak domain), 1 was weak (more than 1 weak domain). All 9 studies with moderate global quality rating, received their single weak rating due to lack of clarity of reporting any study dropouts.

Discussion

We conducted a systematic review to clarify the effects of ~~inflammation~~acute experimental inflammation on cognitive functioning and, more specifically, to determine whether such inflammation was associated with negative biases in emotional processing. ~~Such n~~Negative biases in emotional processing are thought to be of central importance in the development and maintenance of depression. We identified 12 independent studies that used controlled experimental designs to compare the effects of ~~acute inflammation~~acute experimental inflammation on a wide variety of tests of cognitive, social and emotional processing, at varying times following the acute inflammatory challenge

* Calculated from data presented based on the approximate IL-6 molecular weight of IL-6 being 21,000 Daltons,)

We found no convincing evidence from these that acute ~~inflammation~~experimental inflammation was associated in any changes to attention or executive functioning. Positive findings were not supported in the majority of studies. Interestingly, one study provoking ~~inflammation~~acute experimental inflammation with Hepatitis B vaccination and measuring attention over a more prolonged period, did suggest improved performance on the Stroop task, after several days. This could be a chance finding, though it could also indicate that differences in methods of administration of the inflammatory challenge, the magnitude of the inflammatory response and / or differences in the timing of the cognitive assessments might account for differences in observed effects, as has been suggested in previous reviews[43]~~more prolonged inflammation provokes changes to attention after a number of days to weeks. Such findings may not have been detected in the majority of studies due to the very acute nature of the inflammatory challenge~~. More studies are required to investigate this effect.

Studies assessing memory reported more mixed results that could not easily be attributed to differences in study methodology. Whilst a number of interesting changes to memory were reported, that could indicate some potentially important cognitive responses to ~~inflammation~~ acute experimental inflammation, we identified no consistent patterns of effect. Further research is needed, using systematic variations in the dose of inflammatory stimulant, and more consistent application of neurocognitive tests of memory to facilitate comparison across studies.

Studies including measures of social and emotional processing provided the most consistent findings, though these were still quite mixed. Four of the 5 studies, showed an impact of ~~inflammation~~acute experimental inflammation on measures of social / emotional processing. ~~Inflammation~~Acute experimental inflammation caused feelings of social disconnectedness, which could reflect subjective experiences associated with changes in emotional processing. ~~Inflammation~~Acute experimental inflammation changed behavioural and neurological responses to emotional faces. The mixed effects of ~~inflammation~~acute experimental inflammation on response to reward versus loss experiences, and the counter-intuitive finding that low dose but not high dose endotoxin impaired memory for emotional faces require clarification in future studies.

Our review has a number of methodological strengths. First, we conducted thorough searches of 3 electronic databases, which were supplemented with forwards and backwards citation searching of relevant papers. Two researchers independently screened titles and abstracts, and extracted data from eligible study reports, using standardised data extraction sheets, and compared findings to maximise the reliability of the study identification and the data extraction processes. We only included data from controlled studies in apparently healthy participants, using parallel group or cross-over study designs to control for any confounding effects of medical illnesses, and any influence of environmental factors or practice effects on study findings. Finally, we did not limit our searches for relevant papers by year or language of publication, or by the number or type of cognitive tests included. Previous reviews have shown that acute and chronic inflammation is associated with changes in mood and cognition, though findings have commonly been inconsistent[44-46]. By using robust systematic methodology, our review extends on this earlier work by making explicit the balance of evidence for and against effects of inflammation on different aspects of cognition. Furthermore, our review enables us to systematically assess study quality and to identify how methodological characteristics may have influenced findings of the individual studies, to inform future research.

Our review has a number of limitations that merit discussion. First, despite our thorough searching of electronic databases and reference lists, we identified a small number of studies only, many of which were small in size and included quite a large number of tests of cognitive function, thereby increasing the chances of false positive findings, which must be borne in mind when interpreting the findings from individual studies. Second, due to the heterogeneity of methods used, the findings from the 12 independent studies were very mixed and often difficult to compare directly. More studies are required to evaluate the effects of ~~inflammation~~acute experimental inflammation across all cognitive domains, but with more consistent use of inflammatory stimulants and cognitive assessments to facilitate comparisons across studies. Third, the majority of studies limited their inclusion criteria to young, healthy men, and only 2 studies included women, which reduces the generalisability of the findings of this research.

Findings from the research identified must be considered preliminary due to the variation in methods used and findings reported. However, our findings that acute experimental inflammation causes changes to social and emotional processing are consistent ~~However, we conclude that our findings are consistent~~ with the cognitive neuropsychological model of depression and ~~that~~suggest that ~~proposes that~~ inflammation may contribute~~s~~ to the development and maintenance of depression by provoking negative biases in the processing of socially and emotionally salient information. This causal mechanism might explain a number of important observations from the broader research, including: i) the greatly increased risk of clinical depression among people with chronic physical illnesses[47], and ii) why depression is associated with increased mortality[48-50], morbidity[51,52], and worse health-related quality of life[47] among people with chronic physical illnesses. Furthermore, these findings could indicate that impairments in emotional and social processing could be used as biomarkers to identify individual medical patients who are at risk of poor medical outcomes. Prioritising reduction of inflammation in individuals with such vulnerabilities could have potential to prevent or even treat depression associated with inflammation.

Whilst consistent with the neurocognitive model of depression, we acknowledge that findings from studies included in this review do not prove that changes in mood associated with acute experimental inflammation are the result of changes in social and emotional processing. It remains possible that acute experimental inflammation directly provokes a negative mood shift which in turn causes the observed negative cognitive biases. Clarifications of the exact mechanisms of effect of acute inflammation on mood require further detailed experimental study.

The studies included in this review have investigated the effects of ~~acute inflammation~~acute experimental inflammation on cognition and social / emotional processing over short periods (mostly hours). Whilst our finding contribute to academic debate about possible mechanisms underpinning the effects of inflammation on depression and also indicate future avenues for research, we recognise that the effects of chronic inflammation, as seen in clinical populations, could be completely different in nature and extent. Further research in people in chronic

inflammatory states is required to elucidate mechanisms underpinning the development of depression in clinical populations.

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Figure 1: Cognitive neuropsychological model of depression adapted from Roiser et al 2012[10]

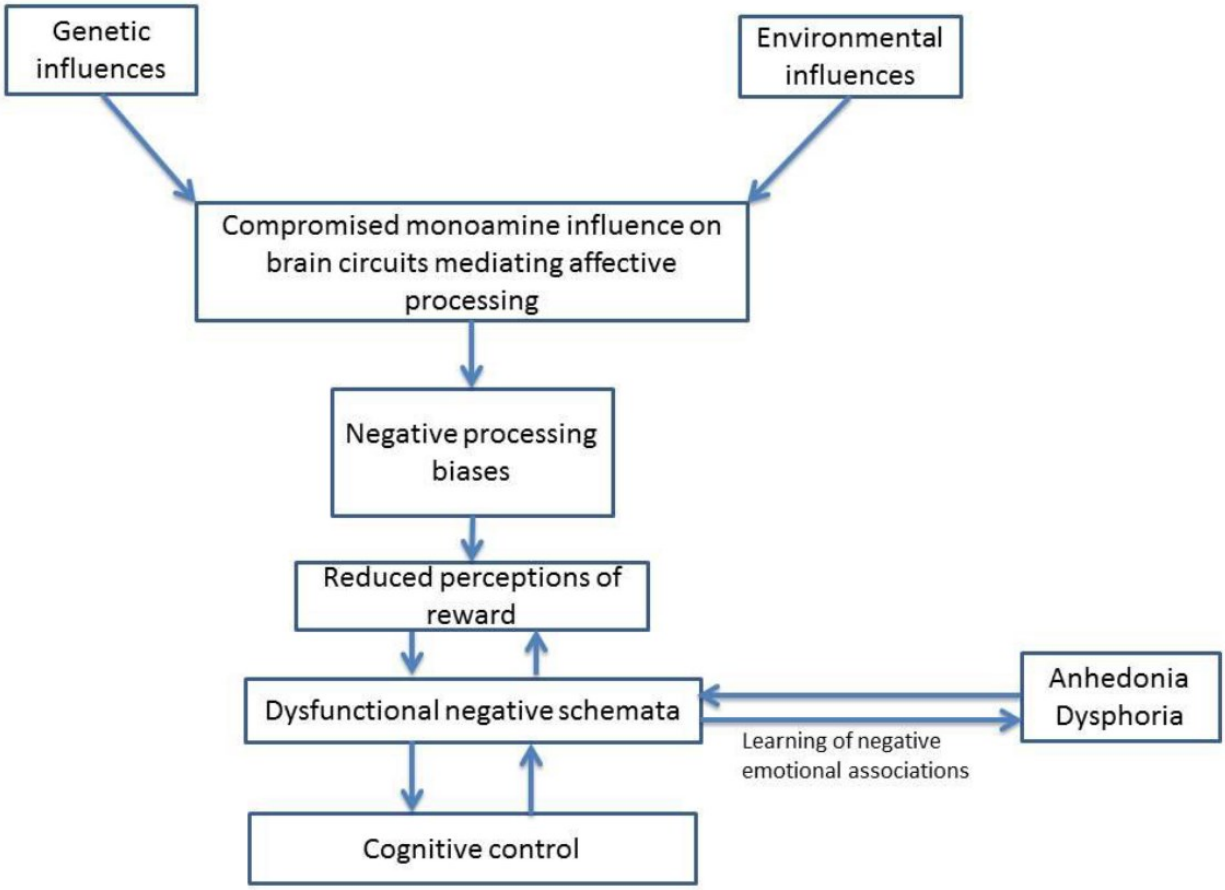

Figure 2 Flow diagram summarising the paper inclusion process

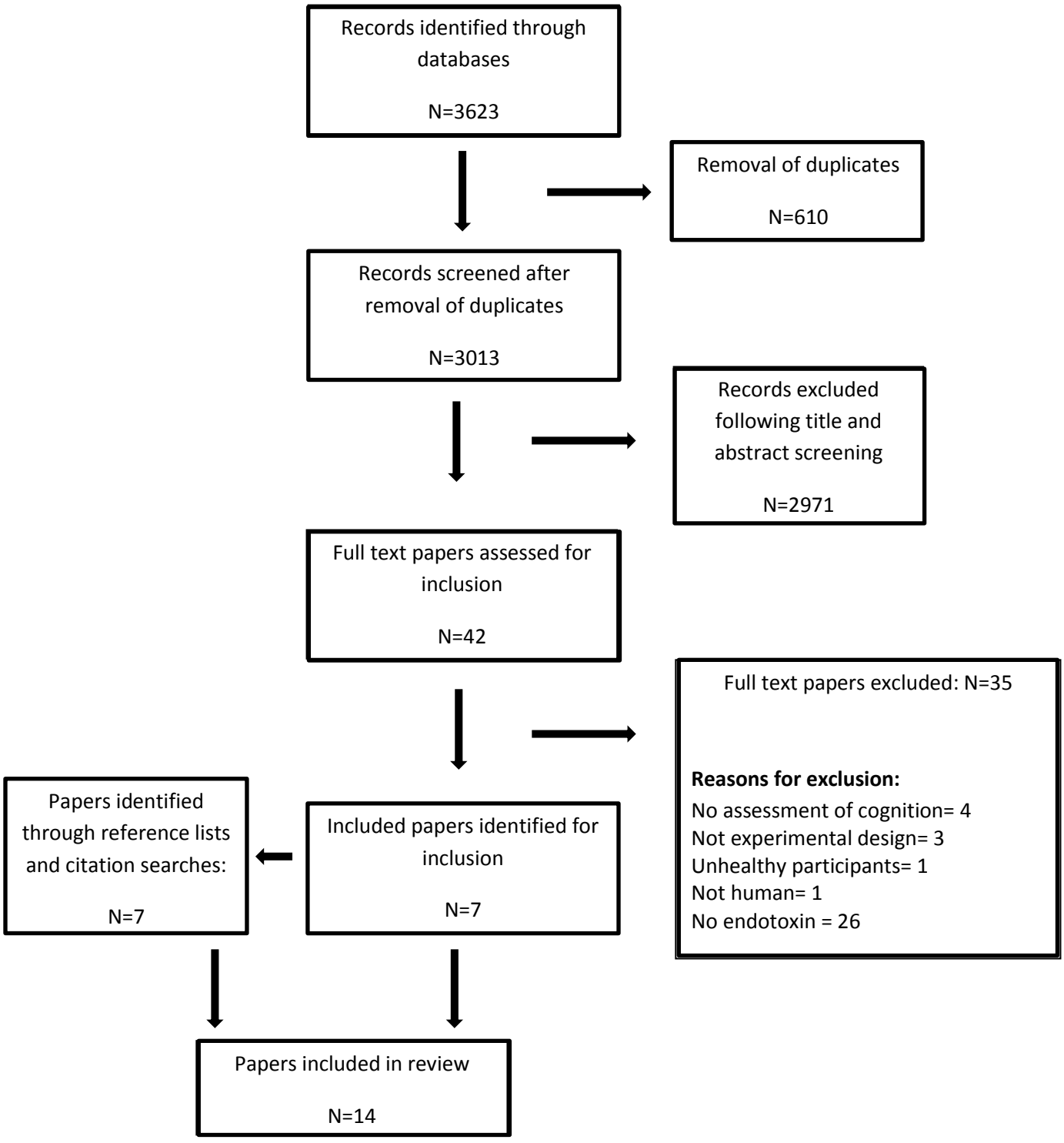

Table 1: Overview table outlining the endotoxin administered, the cytokines examined, and the measurement time points.

Author (year)	Recruitment	No. participants (% Male) [mean age, years]	Trial design	Endotoxin (dose)	Control	Cytokines measured Hours (hrs) post injection)	Cytokines significantly increased
Brydon (2008)[33]	University College London	16 (100%) [24.9]	Randomised, double blind, placebo controlled, cross-over	S.Typhi (0.025mg i.m.)	0.5 ml saline	IL-6, TNF-a , IL-1Ra (3 hrs)	IL-6 (3 hours), endotoxin> placebo. TNF-a and IL-1Ra not significantly increased.
Eisenberger (2010)[31,32]	N/R	39 (48.71) [21.6]	Randomized, double blind placebo controlled	E.coli (0.8ng/kg i.v.)	Same volume saline	IL-6, TNF-a (hrly, 1-6 hrs)	IL-6 (1-5 hrs), TNF-a (1-2 hrs), endotoxin>placebo
Grigoleit (2010)[35]	N/R	24 (100%) [24.9]	Randomized, double blind placebo controlled	E.coli (0.4ng/kg i.v.)	same volume saline	TNF-a, IL-6, IL-10 (1,1.5,2,3,4 ,6 hrs)	IL-6, TNF-a and IL-10 (1.5-3 hrs), endotoxin > placebo.
Grigoleit (2011)[34]	N/R	34 (100%) [24.2]	Randomised, double blind, placebo controlled, cross-over	E.coli (0.8ng or 0.4ng/kg i.v.)	saline	IL-6, TNF-a, IL-10, IL-1Ra (1,1.75,2,3, 4,6 hrs)	TNF-a (1-2hrs),IL-6 (2-3hours), IL-10 (1-3 hrs),IL-1Ra (3-4hrs), endotoxin > placebo. TNF-a, IL-10, IL-1Ra increased high dose endotoxin > low dose
Harrison (2014)[36]	N/R	20 (100%) [24.7]	Randomised, double blind, placebo controlled, cross-over	S.typhi (0.025mg i.m.) at baseline or 4 hours	0.5ml saline	IL-6, IL-1Ra, TNF-a (4,8hrs)	IL-6 and IL-1Ra (4hrs), endotoxin > placebo.
Harrison (2016)[27]	N/R	24 (38%) [27.6]	Randomised, double blind, placebo controlled, cross-over	S.typhi (0.025mg i.m.)	0.5ml saline	IL-6 (3.5hrs)	IL-6 (3.5 hrs)
Krabbe (2005)[37]	N/R	12 (100%)	Randomised, double blind, placebo	E.coli (0.2 ng/kg i.v.)	Saline	TNF-a, sTNF-R, IL-	IL-6(3hrs), TNF-a and IL-1Ra (3-6hrs), sTNF-R(3-4.5hrs),

		[26]	controlled, cross-over			6, IL-1Ra 1.5,3,4.5,6, 24hrs)	endotoxin > placebo.
Kullmann (2014)[38]	University hospital of Essen	18 (100%) [26.4]	Randomised, double blind, placebo controlled, cross-over	E.coli (0.4ng/kg i.v.)	Saline	IL-6, IL-10, IL-1Ra, TNF-a 1.75,3,6,24 hrs)	TNF-a(1.75hrs), IL-6 and IL-10(1.75-3hrs), IL-1Ra(3hrs), endotoxin > placebo.
Moeini (2015)[39]	UCLA and greater Los Angeles community	109 (60%) [24.1]	Randomized, double blind placebo controlled	E.Coli (0.8ng/kg i.v.)	Same volume saline	IL-6, TNF-a (Hrly, 1-6hrs)	IL-6 and TNF-a (1-6 hrs), endotoxin > placebo
Nicoletti (2004)[40]	University of Moderna medical students	14 (100%) [23.6]	Randomized, double blind placebo controlled	HepB vaccine i.m.	Saline	IL-6, TNF-a, HepB Ab (4 days, 4 weeks, 24 weeks, 25 weeks)-a	Hep B Ab (4 days to 25 weeks), vaccination> placebo. No difference in TNF-a or IL-1b detected.
Reichenberg (2001)[4]	University of Munich	20 (100%) [23.7]	Randomised, double blind, placebo controlled, cross-over	S.abortus equi (0.8ng/kg i.v.)	same volume saline	TNF-Rp55, TNF-Rp75, IL-1ra, TNF-a, IL-6 Hrly, 1-10hrs)	TNF-a(1-5hrs), IL-6 (2-4hrs), sTNF-R (2-3hrs), IL-1Ra (2-10hrs), endotoxin > placebo.
[a]Cohen (2003)[30]	Subset of Reichenberg (2001)	10 (100%) [N/R]		Same as above		TNF-a, IL-6	
Van den Boogaard (2010)[41]	N/R	15 (100%) [23]	Non-randomised, controlled	E.Coli (2ng/kg ?i.v.)	Nil	TNF-a, IL-6, IL-1Ra, IL-10 (0.5,1,1.5,2 ,4,8hrs)	TNF-a(1.5hrs),IL-6and IL-10 (2hrs), IL-1Ra(4hrs) Compared to baseline

[a]Cohen used sub-population (n=10) of Reichenberg study, N/R = not reported. i.m . = intramuscular; i.v. = intravenous

Table 2: The effect of inflammatory challenge on cognitive functioning.

Tests of Attention and Executive functioning				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Effects of inflammation on cognition**
Reichenberg (2001)	Attention	Digit span forward	1,3,9hours	No effects
Krabbe (2005)	Attention	Digit span forward	baseline,1.5,6,24 hours	No effects
Van den Boogaard (2010)	Attention	Digit span forward	0,2,8hours	No effects
Krabbe (2005)	Attention	Digit symbol test	baseline,1.5,6,24 hours	No effects
Reichenberg (2001)	Attention	Digit symbol test	1,3,9hours	No effects
Van den Boogaard	Attention	Digit symbol test	0, 2,8hours	No effects
Nicoletti (2004)	Attention	Simple reaction time task	0-25 weeks	No effects
Reichenberg (2001)	Attention	Simple reaction time task	1,3,9hours	No effects
Reichenberg (2001)	Attention	Ruff 2& 7 cancellation test	1,3,9hours	No effects
Van den Boogaard (2010)	Attention	[b]PASAT	0,2,8hours	No effects
Reichenberg (2001)	Attention	Continuous performance test	1,3,9hours	No effects
Grigoleit (2010)	Attention	Wechsler memory scale-R attention score	3hours	No effects
[a]Cohen	Attention / executive	Digit span	1,3,9hours	Significant improvement in performance among subjects receiving endotoxin

(2003)	functioning	backward		(p<0.008).
Krabbe (2005)	Attention / executive functioning	Digit span backward	baseline,1.5,6,24 hours	No effects.
Van den Boogaard (2010)	Attention / executive functioning	Digit span backward	0,2,8hours	No effects
Brydon 2008	Attention / executive functioning	Stroop colour-word naming test	3hrs	No effects
Grigoleit (2010)	Attention / executive functioning	Stroop colour-word naming test	1.5hrs	No effects
Nicoletti (2004)	Attention / executive functioning	Stroop colour-word naming test	Across 0-25 weeks	Significant group effect on reaction times(p<0.001) and group x condition interaction = 0.0013. Post hoc, Stroop effect evident in both groups at baseline and 4days (control > placebo), in neither group at 4 weeks, and only in control group at 24 and 25 weeks. Significant group x condition interaction in errors. Post hoc analyses revealed more errors in control group.
Van den Boogaard (2010)	Attention / executive functioning	Stroop colour-word naming test	0,2,8hours	No effects
Krabbe (2005)	Attention / executive functioning	Trails Making test A and B	not specified	No effects
Reichenberg (2001)	Attention / executive functioning	Colour Trails Making Test A and B	1,3,9hours	No effects
Reichenberg (2001)	Executive functioning	Word fluency test	1,3,9hours	No effects
Tests of Memory				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Results**
Grigoleit (2010)	Immediate and delayed memory	Wechsler memory scale-R	3hours	No effects between group on global memory, verbal memory, visual memory, delayed reproduction
Grigoleit (2011)	Working memory	n-back task	2hours	Group x treatment interaction for reaction time(p<0.05). Post hoc test revealed reduced reaction time in high dose group compared to placebo

				(p<0.01) but not low dose. No difference in accuracy of recall
Harrison (2014)	Immediate memory	Virtual reality object location and identity	Baseline,4hours	Significant group x time interaction for object location(p=0.039) but not identity. Post hoc tests showed reduced object proximity at T2 among those receiving endotoxin(p=0.039).
Harrison (2014)	Procedural memory	Mirror tracing task	0,4,8hours	No effects.
Krabbe (2005)	Memory (plus attention and executive functioning)	Letter number sequence test	baseline,1.5,6,24 hours	No effects.
Krabbe (2005)	Immediate and delayed memory	Word list learning	baseline,1.5,6,24 hours	No effects on immediate or delayed memory
Reichenberg (2001)	Immediate and delayed verbal memory	Story recall (immediate and 30 minute recall)	1,3,9 hours	Immediate(p=0.01) and delayed(p=0.03) verbal memory poorer in endotoxin group
Reichenberg (2001)	Immediate memory	Word list learning	1,3,9 hours	Reduced performance on word list learning in endotoxin group(p=0.01).
Reichenberg (2001)	Immediate and delayed non-verbal memory	Figure recall(immediate and 30 minute recall)	1,3,9 hours	Significant reduction in immediate(p=0.008) and delayed recall(p=0.01) of figure items in endotoxin group
Tests of Social and emotional processing				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Results**
Eisenberger (2010)	Social/ emotional processing	Money incentive delay task	2 hours	No effects on successful button hit rates to reward, loss or neutral trials, reaction time of button hits to reward, loss or neutral trials, or money won
Harrison (2016)	Social/ emotional processing	Probabilistic instrumental learning task for monetary reward / punishment	3 hours	Significant inflammation (placebo, vaccine) by valence (reward, punishment) interaction, p=0.029. Evidence of reduced selection of high probability reward and increased avoidance of high probability punishment. Subsequent computational modelling indicated observed effects of inflammation best explained via an association with increased subjective negative value of punishment stimuli (p=0.047). No effect on value of reward stimuli (p=0.359).

Kullmann (2014)	Social/ emotional processing	Reading the mind in the eye	2 hours	No effects on number of correct responses.
Moieni (2015)	Social/ emotional processing	Reading the mind in the eye	2 hours	Subjects receiving endotoxin responded significantly less well to RME task (fewer correct responses)(condition x time interaction, $p<0.01$).
Grigoleit (2011)	Social/ emotional processing (plus delayed memory)	Recall of neutral and emotive images	24 hours	Significant emotionality x treatment x group effect($p<0.001$). Post hoc analyses reveal reduced recall of emotional faces in low dose group compared to placebo($p<0.05$), but not of neutral faces. No significant effect in high dose group
Eisenberger (2010)[c]	Social/ emotional processing	social disconnection	1, 2, 3, 4, 5 and 6 hours	Significant effect of endotoxin (vs placebo) on measures of social disconnectedness at2 ($p<0.001$), 3 ($p=0.05$), and 4 hours ($p <0.05$), which remained significant after controlling for increases in physical sickness symptoms.
Moieni (2015)	Social/ emotional processing	social disconnection.	2 hours	Significantly more feelings of social disconnection in the experimental group (group x time interaction, $p<0.001$).

[a]Cohen (2003) used sub-population (n=10) of Reichenberg study. [b]PASAT = Paced Auditory Serial Addition Test

[c]Reported in Eisenberger and colleagues[32]

Table 3 Assessment of quality of the 11 independent studies included

Study	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Intervention integrity	Analyses	Global rating
Brydon (2008)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Eisenberger (2010)	Moderate	Strong	Strong	Strong	Moderate	Weak	Good	Appropriate	**Moderate**
Grigoleit (2010)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Grigoleit (2011)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Harrison (2014)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Harrison (2016)	Moderate	Strong	Strong	Strong	Strong	Strong	Good	Appropriate	**Strong**
Krabbe (2005)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Kullmann (2014)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Moeini (2015)	Moderate	Strong	Strong*	Strong	Strong	Strong	Good	Appropriate	**Strong**
Nicoletti (2004)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Reichenberg (2001)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Van den	Moderate	Strong	Weak	Weak	Strong	Weak	Poor	Appropriate	**Weak**

boogaard (2010)									

***Confounders component rated on information cited in: Moeini et al. (2015)[42]**

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Appendices/ supplementary material

Medline search strategy

1. exp Inflammation/

2. exp Cytokines/

3. exp Interleukins/

4. interleukin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. exp Neuropsychological Tests/

6. exp Cognition/

7. exp Cognition Disorders/

8. 1 or 2 or 3 or 4

9. 5 or 6 or 7

10. 8 and 9

Table S1: **Specific tests of neurocognitive functioning used in the included studies**

	Stroop task	Simple reaction task	Implicit facial recognition task	WAIS 111 digit span F	WAIS 111 digit span B	WAIS 111 digit symbol test	PASAT[1]	Word list	Story recall	Figure recall	Ruff 2& 7 cancellation test	Continuous performance test	Colour Trail Making Test A&B test	Trail Making Test A&B test	Word fluency test	Letter no. sequence test	WMS-R	Spatial mem task (virtual reality)	Procedural mem task (tracing shape in mirror)	Money incentive delay task	Probabilistic instrumental learning task for monetary	Social disconnection	Reading the mind in the eye	Emotional processing task with neutral and emotive images	n-back tasks (2 back version)
Bryon (2008)	✓																								
Nicoletti (2004)	✓	✓																							
Van den boogaard (2010)	✓			✓	✓	✓	✓																		
Reichenberg (2001)		✓		✓		✓		✓	✓	✓	✓	✓	✓		✓										
Cohen (2003)				✓	✓				✓		✓														
Krabbe (2005)				✓	✓	✓		✓						✓		✓									
Grigoleit (2010)	✓																✓								
Harrison (2014)																		✓	✓						
Eisenberger (2010)																				✓					
Harrison (2016)																					✓				
Moieni (2015)																						✓	✓		
Kullmann (2014)																							✓		
Grigoleit (2011)																								✓	✓

[1]Paine et al used modified version of PASAT

Table S2: The effect of inflammatory challenge on cognitive functioning.

Tests of Attention and Executive functioning				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Effects of inflammation on cognition**
Reichenberg (2001)	Attention	Digit span forward	1,3,9 hours	No effects between endotoxin and control groups[1]
Krabbe (2005)	Attention	Digit span forward	baseline, 1.5,6,24 hours	No effects between endotoxin and control groups[1]
Van den Boogaard (2010)	Attention	Digit span forward	0,2,8 hours	No effects between endotoxin and control | | t=0hrs | t=2hrs | t=8hrs | Between group comparison | | Endotoxin | 11(1) | 12(1) | 11(1) | P=0.81 | | Control | 10(2) | 11(1) | 11(2) | |
Krabbe (2005)	Attention	Digit symbol test	baseline,1.5,6,24 hours	No effects between endotoxin and control groups[1]
Reichenberg (2001)	Attention	Digit symbol test	1,3,9 hours	No effects between endotoxin and control groups[1]
Van den Boogaard	Attention	Digit symbol test	0, 2,8 hours	No effects | | t=0hrs | t=2hrs | t=8hrs | Between group comparison | | Endotoxin | 87(3) | 99(4) | 101(3) | p=0.53 | | Control | 98(14) | 108(17) | 112(19) | |
Nicoletti (2004)	Attention	Simple reaction time task	0 to 25 weeks	No effects between Hep B vaccinated and controls 179ms vs 174ms(F=0.17, p>0.6).
Reichenberg (2001)	Attention	Simple reaction time task	1,3,9 hours	No effects between endotoxin and control groups[1]
Reichenberg (2001)	Attention	Ruff 2& 7 cancellation test	1,3,9 hours	No effects between endotoxin and control groups[1]
Van den Boogaard (2010)	Attention	[b]PASAT	0,2,8 hours	No effects | | t=0hrs | t=2hrs | t=8hrs | Between group comparison |

				Endotoxin: 49(2); 50(2); 56(2); p=0.07 Control: 50(7); 54(4); 54(5)
Reichenberg (2001)	Attention	Continuous performance test	1, 3, 9 hours	No effects between endotoxin and control groups[1]
Grigoleit (2010)	Attention	Wechsler memory scale-R attention score	3 hours	No effects between endotoxin and control groups (p=0.93)
[a]Cohen (2003)	Attention / executive functioning	Digit span backward	1, 3, 9 hours	Significant improvement in performance among subjects receiving endotoxin (F=12.3, p<0.008).
Krabbe (2005)	Attention / executive functioning	Digit span backward	baseline, 1.5,6,24 hours	No effects[1].
Van den Boogaard (2010)	Attention / executive functioning	Digit span backward	0, 2,8 hours	No effects t=0hrs; t=2hrs; t=8hrs; Between group comparison Endotoxin: 8(1); 9(1); 9(1); p=0.65 Control: 9(2); 9(1); 9(2)
Brydon 2008	Attention / executive functioning	Stroop colour-word naming test	3 hrs	No effects between endotoxin and control groups: response time (p=0.31), errors (p=0.79).
Grigoleit (2010)	Attention / executive functioning	Stroop colour-word naming test	1.5 hrs	No effects between endotoxin and control groups (F=0.17, p=0.69)
Nicoletti (2004)	Attention / executive functioning	Stroop colour-word naming test	Across 0 to 25 weeks	Significant group (vaccination vs control) x condition (congruent vs incongruent tests) interaction (F=8.3, p< 0.0013. Post hoc, Stroop effect evident in both groups at baseline and 4days (control > placebo), in neither group at 4 weeks, and only in control group at 24 and 25 weeks. Significant group x condition interaction in errors (F=13.4, p<0.003). Post hoc analyses revealed more errors in control group (3% vs 5.9%, p<0.05).
Van den Boogaard (2010)	Attention / executive functioning	Stroop colour-word naming test	0,2,8 hours	No effects t=0hrs; t=2hrs; t=8hrs; Between group comparison Endotoxin: 75(6); 65(4); 64(4); 0.23 Control: 67(10); 62(12); 61(11)
Krabbe (2005)	Attention / executive functioning	Trails Making test A and B	not specified	No effects between endotoxin and control groups[1]

Reichenberg (2001)	Attention / executive functioning	Colour Trails Making Test A and B	1, 3, 9 hours	No effects between endotoxin and control groups[1]
Reichenberg (2001)	Executive functioning	Word fluency test	1, 3, 9 hours	No effects between endotoxin and control groups[1]
Tests of Memory				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Results**
Grigoleit (2010)	Immediate and delayed memory	Wechsler memory scale-R	3 hours	No effects between groups on global memory (p=0.99), verbal memory (p=0.60), visual memory (p=0.59), delayed reproduction (p=0.97)
Grigoleit (2011)	Working memory	n-back task	2 hours	Group x treatment interaction for reaction time (F=4.7, p<0.05). Post hoc test revealed reduced reaction time in high dose group compared to placebo (504.9 (71.5)ms vs 532.5(59.3), t=3.2, p<0.01) but not low dose [530.7(58.2) vs 532.6(60.3)]. No difference in accuracy of recall (F=0.2, p>0.05).
Harrison (2014)	Immediate memory	Virtual reality object location and identity	Baseline,4 hours	Significant group x time interaction for object location (F=5.0, p=0.039) but not identity (F=0.66, p=0.43). Post hoc tests showed a greater reduction in object proximity at T2 among those receiving endotoxin (-0.1 vs 0.23m^{-1}, t=2.2, p=0.039).
Harrison (2014)	Procedural memory	Mirror tracing task	0,4,8 hours	No significant group x time interaction (F=1.0, p=0.33)
Krabbe (2005)	Memory (plus attention and executive functioning)	Letter number sequence test	baseline,1.5,6, 24 hours	No effects between endotoxin and control[1].
Krabbe (2005)	Immediate and delayed memory	Word list learning	baseline, 1.5, 6, 24 hours	No effects on immediate or delayed memory (group x time interaction, p=0.12)
Reichenberg (2001)	Immediate and delayed verbal memory	Story recall (immediate and 30 minute recall)	1, 3, 9 hours	Immediate [standardised mean difference (SMD)=0.62, p=0.01] and delayed (SMD=0.55, p=0.03) verbal memory poorer in endotoxin group
Reichenberg (2001)	Immediate memory	Word list learning	1, 3, 9 hours	Reduced performance on word list learning in endotoxin group (SMD=0.61, p=0.01).
Reichenberg (2001)	Immediate and delayed non-verbal memory	Figure recall(immediate and 30 minute	1, 3, 9 hours	Significant reduction in immediate (SMD=0.7, p=0.008) and delayed recall (SMD = 0.64, p=0.01) of figure items in endotoxin group

		recall)		
Tests of Social and emotional processing				
Author	**Function tested**	**Specific Test(s)**	**Comparison**	**Results**
Eisenberger (2010)	Social/ emotional processing	Money incentive delay task	2 hours	No effects on successful button hit rates to reward, loss or neutral trials (p's>0.25), reaction time of button hits to reward, loss or neutral trials (p's>0.59), or money won (t=1.5,p=0.14).
Harrison (2016)	Social/ emotional processing	Probabilistic instrumental learning task for monetary reward / punishment	3 hours	Significant inflammation (placebo, vaccine) by valence (reward, punishment) interaction, F=5.48, p=0.029. Post hoc t-tests, evidence of reduced selection of high probability reward (p=0.195) and increased avoidance of high probability punishment (p=0.071). Subsequent computational modelling indicated observed effects of inflammation best explained via an association with increased subjective negative value of punishment stimuli (paired t = -2.107, p=0.047), with no effect on value of reward stimuli (paired t= 0.938, p=0.359)
Kullmann (2014)	Social/ emotional processing	Reading the mind in the eye	2 hours	No effects on number of correct responses between endotoxin and control groups [11.5(0.5)[2] vs 11.2(0.6)[2]
Moieni (2015)	Social/ emotional processing	Reading the mind in the eye	2 hours	Subjects receiving endotoxin responded significantly less well to RME task (fewer correct responses) - condition x time interaction (F=12.2, p<0.01) and also controlling for i) feelings of sickness (F=9.0, p<0.01), ii) controlling for depression (F=10.7, p<0.01) and iii) controlling for social disconnection (F=10.4, p<0.01).
Grigoleit (2011)	Social/ emotional processing (plus delayed memory)	Recall of neutral and emotive images	24 hours	Significant emotionality x treatment x group effect (F=26.3, p<0.001). Post hoc analyses reveal reduced recall of emotional faces in low dose group compared to placebo [6.4(2.4) vs 7.8(2.4), t=2.9, p<0.05], but not of neutral faces. No significant effect in high dose group emotionality x treatment x group effect F=1.29,p>0.05) [emotional faces 8.5(1.8) vs 8.5(1.30); neutral faces 5.9(2.00 vs 6.8(1.7), t=2.1, p=0.1)].
Moieni (2015)	Social/ emotional processing	social disconnection.	2 hours	Significantly more feelings of social disconnection in the experimental group (group x time interaction, F=15.9, p<0.001).

[1]No numerical results presented

[2]Standard errors

SMD = Standardised Mean Difference effect size (Cohen's d)

Table S3 Assessment of quality of the 11 independent studies included

Study	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Intervention integrity	Analyses	Global rating
Brydon (2008)	Moderate	Strong	Strong	Strong	Weak	Weak	Good	Appropriate	**Weak**
Eisenberger (2010)	Moderate	Strong	Strong	Strong	Weak	Weak	Good	Appropriate	**Weak**
Grigoleit (2010)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Grigoleit (2011)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Harrison (2014)	Moderate	Strong	Strong	Strong	Weak	Weak	Good	Appropriate	**Weak**
Harrison (2016)	Moderate	Strong	Strong	Strong	Moderate	Strong	Good	Appropriate	**Strong**
Krabbe (2005)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Kullmann (2014)	Moderate	Strong	Strong	Strong	Weak	Weak	Good	Appropriate	**Weak**
Moeini (2015)	Moderate	Strong	Strong[a]	Strong	Weak	Strong	Good	Appropriate	**Moderate**
Nicoletti (2004)	Moderate	Strong	Weak	Strong	Weak	Weak	Good	Appropriate	**Weak**
Reichenberg (2001)	Moderate	Strong	Strong	Strong	Strong	Weak	Good	Appropriate	**Moderate**
Van den boogaard (2010)	Moderate	Strong	Weak	Weak	Strong	Weak	Poor	Appropriate	**Weak**

[a]**Confounders component rated on information cited in: Moeini et al. (2015) Sex Differences in Depressive and Socioemotional Responses to an Inflammatory Challenge: Implications for Sex Differences in Depression. Neuropsychopharmacology, 40(7):1709-16.**