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Review article

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

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ABSTRACT

Objective: The cognitive neuropsychological model of depression proposes that negative biases in the processing of emotionally salient information have a central role in the development and maintenance of depression. We have conducted a systematic review to determine whether acute experimental inflammation is associated with changes to cognitive and emotional processing that are thought to cause and maintain depression.
Methods: We identified 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 references were identified, reporting findings from 12 independent studies on 345 participants. Methodological quality was rated strong or moderate for 11 studies. 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 of i) attention/executive functioning, ii) memory and iii) social/emotional processing. Studies found mixed evidence that acute 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; reduced perception of emotions, increased avoidance of punishment/loss experiences, and increased social disconnectedness).
Conclusions: Acute experimental inflammation causes negative biases in social and emotional processing that could explain observed associations between inflammation and depression.

1. 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 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 Fig. 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

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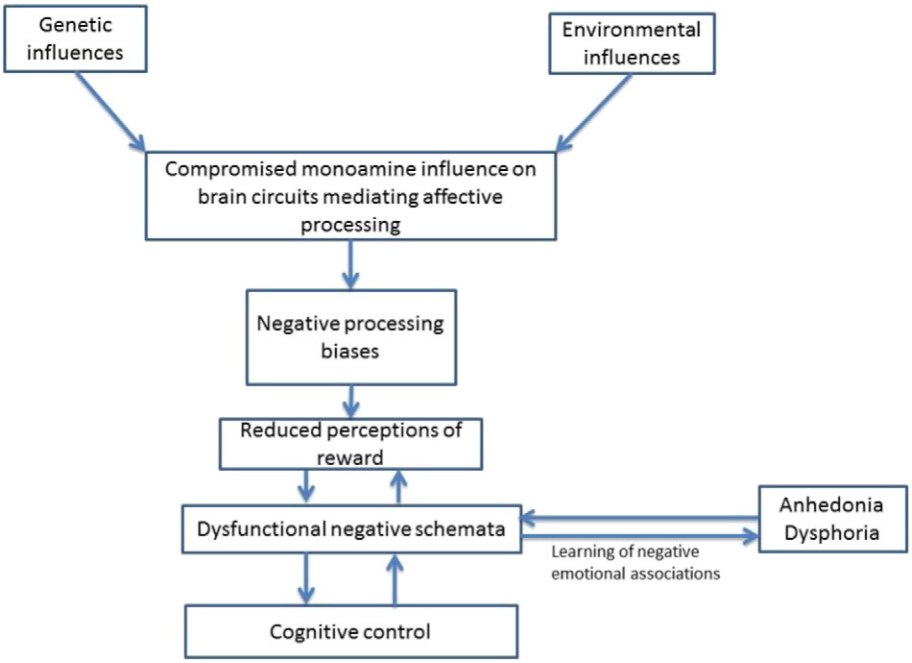

Fig. 1. Cognitive neuropsychological model of depression adapted from Roiser et al. [10].

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. the processing of emotionally and socially salient information (henceforth social/emotional processing).

2. Methods and materials

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

2.1. Inclusion criteria

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

2.1.1. Population

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

2.1.2. 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.

2.1.3. 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.

2.1.4. 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 standardised 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.

2.1.5. 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.

2.1.6. 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–