Hemispheric Lateralisation and Immune Function: A Review

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Abstract

Past studies have examined relationships between hemispheric lateralisation (HL) and functioning of the immune system. However, there has been no up-dated systematic review of this research area. This article reviews relevant published studies, evaluates study quality and effect sizes. Eleven studies were selected: three revealing a relationship between weaker left hemisphere function and poorer immune function, three describing a relationship between weaker right hemisphere function and stronger immune functioning, and five describing both relationships. Mean effect-size of the studies was r = 0.543. Collectively, studies point at left-HL and stronger immunity relationships. Limitations, mechanisms and clinical implications are discussed.

Keywords: Hemispheric Lateralisation; Immune Function; Brain to Immune Communication; Immunomodulation; Humans; Diseases

1. Introduction

Neuroimmunology has uncovered progressively over the last 3 decades the bi-directional manner of communication between the central nervous system (CNS) and immune system (Banks, 2004; Bellinger *et al*., 2008; Besedovsky & del Ray, 1996; Butts & Sternberg, 2008; Ferone *et al.*, 2006; Webster *et al.*, 2002; Wrona, 2006). The immune system communicates with the CNS once an infection has been encountered in the periphery, initiating *sickness behaviour*, providing optimum behavioural conditions to facilitate immune defence and recovery (Banks, 2004; Besedovsky & del Ray, 1996, 2007; Hopkins, 2007; Konsman *et al.*, 2002; Rivest, 2003; Vollmer-Conna *et al.* 2004; Wrona, 2006). One important form of immune-to-brain communication is via the vagal nerve, especially in low levels of peripheral inflammation (Tracey, 2002). The CNS-immune communication is mainly done via sympathetic and neuroendocrine pathways, (Bellinger *et al.*, 2008; Besedovsky & del Ray, 1996; Butts & Sternberg, 2008; Ferone *et al.*, 2006; Neveu, 1988; Webster *et al.*, 2002; Wrona,2006). Receptors for various hormones, neuropeptides and neurotransmitters have been found to be expressed on the surface of many immune cell types (Basu & Dasgupta, 2000; Ferone *et al.*, 2006; McKenna *et al.*, 2002; Webster *et al.*, 2002). Organs of the lymphatic system, such as bone marrow, thymus, spleen, mucosal lymphoid tissues and lymph nodes, have been demonstrated to be innervated by autonomic fibers – mainly of the sympathetic division, but parasympathetic involvement has been described as well (Bellinger *et al.* 2006; 2008; Quan & Banks, 2007; Wrona 2006). Evidence of CNS-immune relations also comes from neurophysiological observations concerning hemispheric lateralisation (HL),

which may help explain some individual differences in brain-immune associations (Neveu, 1988; 1991; 1992). The HL-immune relationship is the topic of this article.

Differential CNS communication with the Immune System – Hemipsheric Lateralisation

How the CNS influences the immune system can depend on many factors, one of which is hemispheric lateralisation (HL). The two hemispheres of the human brain have different functional specialisations, and it is well known that one of the hemispheres will be dominant compared to the other (Cerqueira *et al.*, 2008; Hugdahl, 2000; Neveu, 1988, 1991, 1992). The two hemispheres of the brain are known to act differentially upon behaviour, psychiatric and neurological disorders and immunity (Neveu, 1992). Experimental studies in animals across the last two decades have demonstrated that unilateral damage or stimulation to either the left or right hemispheres of the brain result in opposite immunological reactions (Moshel *et al.*, 2005; Neveu, 1988, 1991, 1992; Neveu *et al.*, 1991). Damage to the left hemisphere results in the depression of immunological parameters such as T-lymphocyte proliferation, natural killer cell activity (NKCA), IL-2 production and production of Immunoglobulin G antibodies (Goldstein *et al.*, 2002; Neveu, 1988, 1991, 1992, Neveu *et al.*, 1991). Damage to the right hemisphere can produce either no immunological change, or even enhance activity of certain immune parameters (Goldstein *et al.,* 2002; Neveu, 1988, 1991, 1992). Furthermore, using unilateral transcranial magnetic stimulation revealed that stimulation of the left temporo-parieto-occipital cortex temporarily increased production of thymic $CD4^+$ and $CD8^+$ lymphocytes, while stimulation of the right hemisphere decreased their levels (Moshel *et al.*, 2005).

Geschwind and Behan (1982) developed a theory based on the association of prenatal testosterone exposure and what they termed "anomalous dominance" (ie. right sided "abnormal" language lateralisation). Observing higher incidences of left-handedness amongst individuals with developmental and immune disorders, Geschwind and Behan hypothesised that this anomalous dominance was a contributor for variation in susceptibility to illnesses (Geschwind & Behan, 1982; Morfit & Weekes, 2001). This theory was supported through large population surveys of left handed individuals, and studies of sinistrality in patients with migraine and immune disorders (Geschwind & Behan, 1982). Whilst vital to the investigation of HL's effects on immune function, this research had conceptual and methodological flaws, most notably the definition of "anomalous dominance". The latter cannot be determined by handedness alone, and is too broad a concept in itself to be used as a definition of cerebral dominance pattern insomuch as handedness is only one activity that is lateralised and cannot comprise a total asymmetry index (McManus & Bryden, 1991). Furthermore, handedness is very poorly, if at all, correlated with HL, but rather may be indicative of language lateralisation only (Jung *et al.*, 2003; Toga & Thompson, 2003). Moreover, a study using mice has shown that handedness effects on immunity can be abolished with left, but not right, cortical ablation (Neveu *et al.*, 1991), suggesting the involvement of more complex brain organisation. While handedness reflects hemispheric specialization (e.g., left hemisphere specializing in certain linguistic abilities), people may differ in their relative levels of hemispheric ***activation*** (Davidson *et al.*, 1999), which we refer to here as hemispheric lateralisation (HL) or cerebral activation asymmetry.

The purpose of this review

Using electroencephalograms (EEG) and neuroimaging techniques, as well as neuropsychological tests assessing specific brain functions, we can test more precise relationships between the CNS and immune systems, with particular emphasis on HL and immunity. To date, there have been no systematic reviews of the research on the relationship between HL and immunity, nor do we know the magnitude of such a relationship. The present review aims to synthesize the currently available research, assess its methodological quality and effect sizes, and interpret the findings with a view to future advancements in the research area and its clinical implications.

2. Method

Literature Search

A computer-based search was conducted for the present review from the following databases; OVID, CINAHL, EBSCOhost EJS, Ingenta Journals, NCBI PubMed, Science Direct, Highwire Press, Scopus, Springer Link, Taylor & Francis Journals and Wiley Interscience. The key search terms of "lateralisation" and "lateralization" were combined with the Boolean operator OR; in conjunction with AND for the secondary terms of "immune function", "T cells", "natural killer cells", "immunity", "cytokines", "lymphocytes". Another strategy of using as keywords "cerebral asymmetry", "stroke", "epilepsy", "traumatic brain injury", and "cerebral lesion" were combined with the Boolean operator OR, in conjunction with AND for the secondary terms listed previously. The time period selected was to encompass the years from 1982 (the year of the Geschwind *et al.* study) to 2010. Only full text articles were identified for inclusion into the review. There were no systematic

reviews or meta-analyses currently available on this topic in humans. All identified articles were scrutinized for other relevant articles in their reference lists.

Selection Criteria

Studies were selected based upon their relevance to humans, and their relevance to the relationships between lateralisation and aspects of immune functions, using either a cross-sectional or experimental design. Studies that did not primarily assess the relationship were also considered if their data examined this as a secondary analysis. The study was limited to papers in English or French, though all studies obtained were ultimately in English. Studies that were excluded include those using handedness as a sole measure of lateralisation (because of the aforementioned conceptual incongruence between handedness and HL (Jung *et al.*, 2003; Toga & Thompson, 2003)), and those using clinical conditions that resulted in more complications than just lateralisation (eg. cerebral palsy). Studies that examined immunity without direct immunological measures (ie. self-report health surveys) were excluded.

Quality Assessment

The quality of each of the articles was assessed using a five-item checklist, with scores ranging from 0 to 18, with relevant predefined criteria. The criteria were adapted to suit the present data, and were derived from quality assessment frames such as can be found in Mols *et al*. (2005) and Borghouts *et al.* (1998). The categories viewed essential to ensuring a good standard of methodological quality (internal validity) concerned control over third variables and the statistical treatment. Those third variables that can affect the relationship between the brain and the immune

system were demographic (e.g., age), psychological (e.g., chronic stress), physiological or neurological (e.g., inflammatory diseases), and an extensive list of these variables was established. Another essential criterion of quality assessment was the study conclusions: whether correctly derived from the study design and results. One investigator (RS) assessed all articles and another (YG) assessed five of the articles for inter-rater reliability. The quality criteria are presented in Figure 1.

Extracted information

This included the research team and year of publication, the sample, the types of HL and immunological tests conducted, the research design, and the observed results.

Effect Size Assessment

Effect size calculations were undertaken only on the main tests of the relationship between HL and immune functions. These were calculated utilising the reported statistical information relevant to the statistical tests used for each main relationship or effect studied – where available. Mean effect sizes across study type (cross-sectional, semi-experimental) and across all studies were calculated in order to yield a single standard for comparison across studies. Although effect size analysis is usually the remit of meta-analyses, the present data were too heterogeneous to merit this sort of analysis, with wide varieties of outcome measures and methodology. In light of this heterogeneity, it was decided that examining effect sizes would provide a reliable means of comparing and summarising statistical strength across studies.

3. Results

Study Characteristics

Seventeen studies were initially identified as fulfilling the overall criteria of examining a relationship between HL and immune function. After all exclusion criteria were applied to the identified literature, 11 articles remained eligible for inclusion in the present review. Eight studies used clinical samples (eg. stroke, epilepsy patients) and three used healthy samples. Eight of the studies used quasi-experimental or experimental methodologies; and three used cross-sectional or prospective methodology. A summary of the reviewed studies can be found in Table 1.

Quality Assessment

The correlation between the two evaluators for the quality assessment of the five articles dually rated was 0.98. The quality assessment figures are presented in Table 1. The mean quality assessment mark was under 50% (7.909, SD= 1.136) of the total possible score, 17. The general low level of methodological quality of the studies was mainly due to their lack of control over third variables, limited sample sizes and questionable conclusion validity.

Effect Sizes

Effect sizes (*r*) were calculated for the main effects of nine of the reviewed studies for which relevant data were available for these calculations. A mean effect size for the HL-immunity relationship was calculated per study, across its various tests. The effect sizes were interpreted using Cohen's (1988) criteria for small ($r > 0.1$), medium ($r > 0.3$) and large ($r > 0.5$) effects. Using these criteria, six of the nine studies (67%) had large mean effect sizes for their main effects; one showed a medium effect size; and

two a small effect (Table 2). The mean effect size (*r*) of the HL-immunity relationship for the main effects of the assessed studies was 0.543, which is designated as a large effect size. Of the three cross-sectional studies reviewed, two provided sufficient data to process effect size analyses; the mean effect size for these two studies was 0.564 (range .540 - 0.588), a large effect size. Of the eight remaining studies that employed either experimental or quasi-experimental designs, seven provided sufficient numerical data to conduct effect size calculations. The mean effect size for this group of studies was 0.572 (range 0.161 – 0.814), which is also a large effect size. This effect size refers to the overall differential effect of lateralisation on immunity. A summary of the effect sizes obtained for the assessed studies can be found in Table 2.

Quasi-Experimental and Experimental Data

These studies involved either direct manipulation of variables (Davidson *et al.*, 1999; Clow *et al.*, 2003) or used patient groups that demonstrated atypical lateralisation (Koch *et al.*, 2006; Ivashkova *et al.*, 2002; Meador *et al.*, 1999; 2004; Tarkowski, *et al.*, 1995; 1998). The articles are presented chronologically, according to the year of publication.

Tarkowski et al., 1995

Using patients of minor, major and progressive stroke, Tarkowski *et al.* (1995) assessed tuberculin skin reaction, histamine initiated T-cell response, and pokeweed (PW), phytohemagglutanin (PHA) and Concanavalin-A (Con-A) initiated lymphocyte distribution in those with left or right localised brain trauma. Lateralisation of skin response was relative to the clinical categorisation of the stroke, residual motor function and the lateral localisation of the lesion. Patients with left localised lesions

displayed smaller Delayed type hypersensitivity (DTH) responses than those with right lesions, but those with right-sided lesions also demonstrated lateralised peripheral reactions (ie. greater responses on ipsilateral side than contralateral side). The ability to find a HL-immune relationship in such a heterogeneous sample, compared to the more homogenous samples described below, supports the generalised effect of HL on immune function in humans. However, very little control over third variables was done, which is particularly important in patients with cerebral ischemia. Stroke may be indicative of other illnesses that may affect the communication between the brain and immune system, and such illnesses could in themselves be indicative of atypical brain to immune communication (eg. hypertension, diabetes), possibly affecting vagal immune-modulation. No control over psychological or cognitive variables relevant to stroke, that may be related with either HL or immune function (e.g., executive functions, depression), was done as well, limiting this study's inferential validity.

Tarkowski et al., 1998

In a follow-up study, the same methodology as Tarkowski *et al.* (1995) was employed, but the clinical sample was split into three groups (early stroke, early stroke with retest of parameters in the subacute phase, and chronic stroke). This study replicated the former findings, but also showed that in the right trauma localised early stroke sample, larger DTH responses to immune challengers were seen for both the paretic and contralateral sides compared to those with left stroke. In the chronic phase of stroke, those with right localised ischemia showed a greater response than those with left stroke at the ipsilateral side. This research considered a generally high number of third variables, although there was no control over levels of depression,

anxiety or general mood, which are related to immune function (Kemeny & Schedlowski, 2007), and are clinically relevant in such patient samples.

Davidson et al. 1999

Using healthy students Davidson *et al.* (1999) used emotionally evocative film clips to manipulate natural killer cell activity (NKCA) in left and right lateralised (as determined by electroencephalograph; EEG) participants. NKCA was assessed at an anxiety-neutral time (mid-semester) and at a high anxiety time (exam period). Participants with left frontal-anterior-temporal lateralization had greater NKCA in response to the positive film clips at both times than those with right lateralization. This study thoroughly considered third variables including handedness, caffeine, nicotine and alcohol consumption. However, there was no control for the use of prescription medications, or other illnesses, that may interfere with natural brain or immune system functioning, and this study has a relatively small sample size (n= 24) in comparison to the mean of all studies (n= 47.1). Nevertheless, using a naturalistic stressor (exam stress) and finding higher NKCA in left-HL participants in two contexts suggests that this relationship may be generalizable to various contexts.

Meador et al., 1999

Using patients waiting for epilepsy resection surgery, Meador *et al.* (1999) examined the differences in those receiving surgery at language dominant (DOM, left) and non-dominant (NDOM, right) hemispheres, and several immunological outcomes. Increases in white blood cells (WBC) and decreases in CD8 post-surgery for the DOM group, and increases in CD4 post-surgery for the NDOM group were observed. Overall, aside from with WBC, the immune parameters decreased post-surgery for the

DOM group and increased for the NDOM group, although many of the findings did not attain statistical significance. Of the main effects, only the total pre-operative versus post-operative group analysis of WBC attained significance, the DOM versus NDOM main effect did not reach significance. A string of *post-hoc* tests were employed to elucidate the findings in light of this lack of significance, although it is not clear whether statistical adjustments were made for these multiple comparisons. However, the overall effect observed was in line with right hemisphere functioning being indicative of poorer immune functions. The sample size for this study was relatively small (n=11), and it was heterogeneous due to its clinical nature. There was relatively little third variable control (e.g., comorbid illnesses). The indices of laterality are also less than reliable. Whilst the use of the DOM/NDOM classification is useful to partly understanding the HL of the patients, looking at resections in these categories as opposed to concretely left/right hemisphere, is conceptually problematic as it defines laterality in relation to function or specialisation, rather than to activity and side.

Ivashkova et al., 2002

Three groups of participants were used with this study, a group of subacute stage stroke patients receiving transcranial-electromagnetic stimulation (TeMS) therapy; a reference group of subacute staged stroke patients not receiving TeMS, and a control group of healthy participants also receiving TeMS. A variety of immunological parameters were assessed, along with lymphocyte proliferation to Con-A, PW and PHA before and after TeMS, and proliferation changes were compared to the values observed in the control and reference groups. Lateral localisation of the lesion was directly involved in the type and degree of observed immune alteration. Right

hemispheric stroke was shown to be related to T-cell deficit and disruption of lymphocyte proliferation, whereas left hemispheric stroke was associated with decrease in lymphocyte proliferation only. TeMS resulted in the normalisation of immune values in the group of clinical subjects with right localised lesions. The main limitation of this study is that the researchers used multiple statistical tests, risking a type 1 error, without employing a correction for multiple tests. However, the use of two control groups was a methodological strength. Finally, the duration, frequency and precise location of the TeMS were not reported, which may impact the inferential validity of the findings as these factors affect immunity (Davidson et al., 1999). Analysis of confounder control either methodologically or statistically is difficult to infer, as there were no exclusion criteria or extraneous variable controls mentioned.

Clow et al. 2003

Healthy participants were selected for this study, which involved using repetitive transcranial magnetic stimulation (rTMS) to both hemispheres (on separate occasions) over the temporo-parieto-occipital (TPO) cortex, and assessing salivary Immunogloblin A (S-IgA) changes before and after stimulation. The authors reported that initially rTMS to either hemisphere resulted in an increase in levels of S-IgA. However after accounting for saliva volume, revealing the concentration of S-IgA, the results were further elucidated: left hemispheric rTMS resulted in an increase in S-IgA whereas right resulted in decreases in S-IgA. Nonetheless, with a sample size of just 16 participants, with 3 participants being tested twice meant this preliminary study was relatively small in comparison to the rest under review. Furthermore, it is unclear as to how the data from those participants who were retested was dealt with, which makes validity difficult to assess. The only inclusion criteria mentioned were

that the participants were healthy and right handed, with no mention of exclusion factors or control for third variables. Finally, there was also no "sham" rTMS condition, which could affect the results (Toschi *et al.*, 2009), and the inferences concerning the effects of TMS and HL on immunity. Nevertheless, this is among the only fully within-subjects experimental design and, together with the inclusion of a healthy sample, these results do suggest the possibility of a causal relationship between left-HL and immunity as indexed by S-IgA.

Meador et al., 2004

This research group again used surgical epilepsy patients to examine changes in immune parameters post-surgery, but added a healthy control sample for further analysis. Using lymphocyte counts, responses to mitogen and microbes and histamine skin testing, they also examined the effects of mood (Profile of Mood States; POMS) in the relationship between hemispheric surgery and immune alteration. Left resection patients showed decreases in total lymphocytes, T cells, CD8 and CD4 after resection surgery, while the opposite was observed for the right resection patients. These effects remained stable when POMS was included in the statistical testing. Histamine skin responses showed that left resectioned patients displayed greater right arm wheal responses compared to the right resection patients and control group. Flare responses were reported to decrease after left resection, and increase after right resection. In comparison to the prior Meador *et al.* study (1999), this research included twice as many participants (n=22), but is still below the mean for all of the studies reviewed. The change in methodology from examining differences between DOM and NDOM groups, to differences between left and right resection groups makes the findings more directly relevant to HL. The use of cellular proliferation and histamine reaction

in a control group to account for non-systematic variability in the clinical group, and the examination of psychological variables (mood) demonstrates carefully considered confounders and processes, although no exclusion criteria were detailed. The finding of left resection leading to both reduced cellular (Th1) immunity (decreased T-lymphocytes) and increased allergic responses (greater histamine reaction) is indicative of the left hemisphere being implicated in the modulation of immunity and possibly in certain immune-related illnesses. This association, however, may well be a conflicting one, as Th1 immunity involves the expression of pro-inflammatory cytokines, which would be decreased in this sub-sample, but allergy requires an increase in Th1 immunological response (Webster *et al.*, 2002), so further research is required. Nevertheless, concerning only the lymphocyte data, these results are in line with a left-HL increasing cellular immunity and right-HL having an opposite effect.

Koch et al., 2006

In the most recent of the reviewed studies, this research group again used stroke patients to examine the effects of stroke lateralisation (as verified by magnetic resonance imaging or CT) on C-reactive protein (CRP) and WBC. The authors reported that left hemispheric stroke resulted in an increased variability in both CRP and WBC, and that correlations between these two parameters were only observable in the left-localised stroke patients, suggesting a defecit in immune control after left-sided ischemia. This study was one of the five of all the reviewed articles that included a sample size above the mean value. However, that study only examined the immune parameters of WBC and CRP, which in itself is limited in comparison to other similar studies (eg. Meador *et al.*, 2004). Furthermore, this analysis was also only conducted in the first 24 hours of stroke onset. Stroke in general, regardless of

laterality, has been suggested to cause alterations to lymphocytes, granulocytes and leukocytes, particularly within the first 24 hours of onset (Miller *et al.*, 1991; Vogelgesang *et al.*, 2008), which would necessitate testing HL-immune relationships at periods beyond this phase, as these changes could be partly stroke-related rather than laterality-related. In addition, the authors provided no theoretical rationale for the relationship between CRP and WBC: Is this reflecting the greater variability in those two variables among left-hemisphere people, or does the left hemisphere in general regulate one or both parameter, possibly influencing the other one?

Cross-Sectional or Prospective Data

These studies involved using healthy (Kang *et al.*, 1991) and clinical (Dziedzic *et al.*, 2003; Gruzelier *et al.*, 1996) participants. They are presented in chronological order.

Kang et al., 1991

Using EEG measures, the researchers selected a group of healthy participants who displayed "extreme stable activation", in either the top or bottom quartile of cerebral activation asymmetry (i.e., left or right HL). The researchers examined NKCA, lymphocyte proliferation (to Con-A, PHA and PW) and other immune parameters, whilst also obtaining self-report data concerning frequency of common illnesses in the past 12 months and family history of autoimmune diseases, as well as administering some psychometric scales (anxiety, depression and stress). They reported that higher right frontal activation (as opposed to higher left) resulted in lower levels of NKCA and Immunoglobulin-M, as well as lower lymphocyte proliferation in response to PHA. The immune effects observed could not be accounted for by the health survey, plasma cortisol levels or the psychometric scales. The use of subjective self-report

data concerning health again leaves questions concerning validity of immune related illnesses. Nevertheless, the methodology was thorough including details about viral, fungal and respiratory infections as well as allergies and dermatological status. Control for confounding variables, the selection of participants in the top and bottom quartile for HL, taking details of drug use, including right-handed participants only, and conducting the immunological assessments at an anxiety-neutral time, are all evidence of relatively strict methodology. The small sample of female participants alone also has an impact on the generalisability of the findings, and leaving immunological assessment possibly subject to hormonal influences which were not fully tested or controlled for (Butts & Sternberg, 2008; Kovats & Carreras, 2008; Taub, 2008). Whilst other studies have used female participants where this effect could also be observed, this was the only study to exclusively include female participants, and therefore any gender effects cannot be metered out by the inclusion of male participants who may not display these hormonal influences. The lack of cortisol effects could mean that HL-immunity relationships are dependent on other neuro-endocerine-immune pathways, unrelated to the HPA axis or only unrelated to cortisol. We shall discus this important issue below.

Gruzelier et al., 1996

This study included asymptomatic HIV^{+} patients, and measured their immune outcomes (CD4, CD8) at a follow-up of 36 months in relation to baseline EEG recordings of cerebral laterality and performance on neuropsychological tests assessing right/left brain functions. The experimenters found that greater left hemisphere functioning predicted higher CD4 both at baseline and at follow-up, and that greater right functioning predicted greater immune suppression (CD8). The

sample for this study was small (*n*=27) and was restricted to men of bisexual or homosexual orientation. Today, the largest proportion of HIV transmission across the world occurs in heterosexual activity (Grant & De Cock, 2001; Hansasuta & Rowland-Jones, 2001). The pathogenesis of HIV may depend on biological parameters and socioculturally influenced health behaviours of individuals (ie., comorbid illness, clinic attendance, heavy drug or alcohol use) which cannot be accounted for in such a restricted sample, nor generalised to a wider population (Derdeyn & Silvestri, 2005; Lama & Planelles, 2007; Gifford *et al.*, 2002). Most importantly, the investigators did not statistically control for effects of baseline immune parameters and other confounders (e.g., education, mode of infection, other illnesses, medications) that may affect the autonomic, nerve or immune systems (Cole *et al.*, 2003). All these limitations question the validity of their inferences. Nevertheless, this is among the only studies showing a prospective relation between two different measures of HL and immunity in the context of an illness. But, future studies must replicate it and address its many limitations.

Dziedzic et al., 2003

Using stroke patients and a healthy control group, this research group sought to examine the relationship between stroke location and interleukin (IL)-10, and IL-6. Stroke location and size were assessed using CT scans and the control group was not assessed for any form of lateralisation. The stroke patients showed higher IL-10 and IL-6 levels than the control group. Within the stroke patient group, those with left localised stroke showed higher levels of IL-10, but there was no difference in IL-6. This study exhibited a good level of confounder control, with psychological, physiological and neurological factors all being considered, as well as including a

healthy control group. However, as with Koch *et al.* (2006), the immune measures were taken at around 24 hours after hospital admission, which makes the reliability of the finding of abnormal IL-10 questionable, as this may not be due to laterality *per se*, but possibly also due to the stroke itself. Whilst IL-6 and IL-10 reflect Th1 and Th2 immunity, respectively, a wider panel of immunological assessment would have been useful. Nevertheless, this is one of the only studies examining the relation between HL and cytokines, and results suggest that left HL is related to lower anti-inflammatory activity (IL-10). More studies need to replicate and extend this important issue.

4. Discussion

General conclusions

This systematic review summarises the results of 11 research articles investigating the relationship between hemispheric lateralisation (HL) and immune function. All of the reviewed studies show a relationship between HL and immune function. Three of the 11 (27.27%) studies described a relationship between poorer left versus right hemisphere function and decreased immunity in at least one immune parameter (Dziedzic *et al.*, 2003; Kang *et al.*, 1991; Koch *et al.*, 2006). Three of the 11 (27.27%) studies described a relationship between poorer right versus left hemisphere function and increased immunity in at least one parameter (Davidson *et al.*, 1999; Tarkowski *et al.*, 1995, 1998), in line with the finding of the first three studies. Five of the 11 (45.45%) studies described both relationships of HL and immunity (Clow *et al.*, 2003; Gruzelier *et al.*, 1996; Ivashkova *et al.*, 2002; Meador *et al.*, 1999, 2004). Despite the disparity in methodologies and outcome variables, this suggests that HL, as a neuropsychological phenomenon, plays a key role in the functioning of the immune system in both health and sickness. Importantly, the findings reviewed here can be

synthesised into one direction; namely that the left hemisphere is immunopotentiating, the right is immunosuppressing, and they may be balanced by means of interhemispheric inhibition (IHI). IHI is thought to mainly take place via the corpus callosum (Geffen *et al.*, 1994; Sullivan, 2004), and can explain the changes in immunoregulation following cerebral trauma such as stroke or surgery.

One study extended these relationships to examining more specific areas of the brain within the hemispheres, related to immune function. The Davidson research group revealed that HL in the mid-frontal, parietal and anterior temporal regions was strongly related to higher NKCA, while posterior HL regions of the brain were unrelated to NKCA (Davidson *et al.*, 1999). Other researchers found that immune activity (NKCA and lymphocyte proliferation) is associated with more specific activity in brain regions including the secondary visual, motor and sensory cortices; hippocampus; putamen; thalamus; anterior cingulate cortex; posterior parietal cortex; and several areas of the prefrontal cortex (Lekander *et al.*, 2000; Matsunaga *et al.*, 2008; Ohira *et al.*, 2008; Tashiro *et al.*, 2001; Wik *et al.*, 1998). However, those studies did not test whether HL in such regions is related to immunity.

The mean effect size for the HL-immune relationship we observed was 0.543, which is designated as large. Two studies reported mean effects in the upper quartile (r>0.65) of those available (n=9) (Ivashkova *et al.*, 2002; Tarkowski *et al.*, 1998). These studies were both from the quasi-experimental/experimental category, which provides more validity to such an effect of the HL-immune relationship. The mean effect size for those studies that described a relationship between poorer right versus left functioning and increased immunity (Davidson *et al.*, 1999; Tarkowski *et al.*,

1995; 1998) was higher than the mean effect size for the studies observing the opposite relationship (Dziedzic *et al.*, 2003; Kang *et al.*, 1991; Koch *et al.*, 2006) (0.503, 0.374 respectively). The studies in the present review do show a high proportion of "large" effect sizes. However, attempting to compare studies that have such different independent and dependent variables, methods of data collection, methodological design and samples, can often cloud the main findings due to their disparities. Thus, we chose to focus on overall effect sizes, which can provide an stable and simple means of elucidating combined findings. The fact that 66% of the effect sizes showed "large" effect sizes in the same direction is perhaps the most promising finding of the combined results. This shows that despite the differences in methodology, the relationship between left-HL and enhanced immunity is a robust effect.

In relation to the quality assessment scores, there were three studies that received scores in the upper quartile of the observed range (6-10) (Davidson *et al.*, 1999; Dziedzic *et al.*, 2003; Kang *et al.*, 1991). These studies are of both cross-sectional and experimental design. The common factor amongst these studies is control for third variables from at least two of the designated criteria. All three of the methodologically rigorous studies supported the conclusion that left-HL is related to immune potentiation. The mean quality assessment score of all evaluated studies was under 50% of the total possible score, which suggests that methodology in this subject area is in need of improvement. The main areas that need improvement are control over third variables and inferential validity. More control is required to ensure that the HL-immune relation does not result from variables involving health behaviour (e.g., smoking), gender or co-morbidities known to affect the immune or CNS systems

(e.g., arthritis, infections, early dementia). Attention should also be paid to the immunological outcome measures, and the reasons for choosing them – as these were very rarely attended to in this body of literature. With regard to the conclusions, the main areas of improvement are the contextual evaluation - where each study fits amongst the current literature, and future theoretical and clinical implications.

Possible mechanisms underlying the HL-immune relationships

Cortisol appears not to affect the association between HL and immunity (Kang *et al.*, 1991; Meador *et al.*, 2004). This suggests that the HPA-axis, at least as indexed by cortisol, does not play a role in the HL-immune relationship. There are also established relationships between HL and the stress response, with the right prefrontal cortex being associated with the modulation of the stress response (Cerqueira *et al.*, 2008; Lewis *et al.*, 2007; Sullivan, 2004). An alternative mechanism to explain the HL-immunity relationship may involve the sympathetic adrenal medulla (SAM) system since provision of beta-blockers reduced the HL-immune relationship (Moshel et al., 2005). Future studies need to replicate such studies in humans, and must test the functional and health implications of such mediation.

Another hint for the involvement of the SNS in HL-immune relations comes from the fact that the mean effect size of studies showing weaker right-HL and strong immunity associations was stronger than the mean effect size of studies showing the reverse. This finding is particularly interesting, considering the evidence for the right side of the brain being responsible for sympathetic nervous system (SNS) activity (Bär *et al.*, 2005; Sullivan, 2004; Wittling *et al.*, 1998). This link is relevant to the study by the Dziedzic group (2003), who found an increase in IL-10 amongst those

stroke patients who suffered a left hemispheric infarct (presumably having stronger right-HL). IL-10 is a potent anti-inflammatory cytokine, key to the humoural (Th2) arm of immunity (Besedovsky & del Ray, 2007; Chabot *et al.*, 1999; Webster *et al.*, 2002), and has been suggested to be driven by activation of the SNS (Bellinger *et al.*, 2008; Chabot *et al.*, 1999; Webster *et al.*, 2002). The effects of left brain damage and increased levels of IL-10 could, therefore, be indicative of enhanced activation of the SNS by the right hemisphere. Conversely, this suggests that the left hemisphere inhibits production of anti-inflammatory cytokines and may augment production of pro-inflammatory cytokines. These associations require further investigation to uncover implications on HL and Th1/Th2 immunity in both healthy subjects and brain-damaged patients.

Clinical implications

The study by Gruzelier *et al*. (1996) and a more recent one examining the predictive capacity of HL in symptoms of upper respiratory tract infections (Gidron *et al.*, 2010) demonstrate that the HL-immune relationship has implications for immune-related diseases. This requires further research concerning both prediction of disease risk, prognosis and possible prevention using brain stimulation of the left-PFC for diseases originating from immune-suppression. The extent to which such illnesses may be prevented or ameliorated by left-PFC stimulation has vast implications to 'brain over disease' relationships and to opening new therapeutic approaches. The study by Clow et al. (2003) using rTMS may be one promising method for further investigation in relation to disease prevention. Yet, more sound research is needed to solidify the scientific ground for such interventions.

Some research has uncovered an asymmetry in both peripheral immunity and in diseases. An asymmetry in peripheral cell-mediated immune diseases has been observed in a left-sided prevalence of herpes zoster presentation (Dane, 2009), as well as a greater left-sided reaction to bilateral tuberculin skin tests (Dane *et al.*, 2001). This peripheral cell-mediated asymmetry has also served as an explanation to findings of overall greater right-sided metastases in some gynaecological cancers (Borecki *et al.*, 2007), as well as a higher prevalence of right-sided metastases in malignancies originating on both sides of the body (Borecki *et al.*, 2007). It has been suggested that excessive left side immune reactions may be responsible for controlling left sided metastases, therefore increasing the prevalence of right side spread (Borecki *et al.*, 2007; Dane *et al.*, 2008). However, inconsistencies have been found as well when investigating paired organs. In a study that included over a quarter of a million cancer patients, Roychoudhuri *et al.* (2006) found lung and testicular cancer to have a right-sided prevalence, whereas breast cancer was suggested to be more common on the left (Roychoudhuri *et al.*, 2006). There was very little difference observed bilaterally in kidney and ovarian cancer incidence, however five year survival was shown to be higher in women with left-sided ovarian cancer than those with right-sided tumours (Roychoudhuri *et al.*, 2006). The discrepancy of the overall trend represented by breast cancer was theorized to be due to behavioural and diagnostic reasons, insomuch as the right-handed majority may be more aware of changes in the ipsilateral breast, or that right handedness may cause more movement in the breast, or preference in breast feeding, and therefore affect cancer risk (Roychoudhuri *et al.*, 2006). The extent to which peripheral immune laterality of cerebral HL are responsible for such laterality in disease risk needs further investigation.

Summary & Conclusions

This review outlines 11 studies concerning the relationship between HL and immune function. As the first of its kind, it is predominantly apparent that more research is required in this area to further elucidate findings, and uncover more aspects of this relationship. Further investigation into the specific areas of the brain, as well as lateralization effects (nature, duration, etc.), and their underlying mechanisms, is also clearly needed. The role of the SNS as well as neurotransmitters (e.g., acetylcholine, dopamine) in the HL-immunity relationship needs to be examined. The present literature also brings about interesting questions for neuroimmunology. For example, given the differential and quite robust immunomodulation by HL (see our mean effect size), could lateralisation predict the onset of immune-related illness? The evidence from the Gruzelier group (Gruzelier *et al.,* 1996) and the recent study by Gidron *et al.* (2010) indicates this may be possible. If such a relationship were discernable, then it would be reasonable to suggest that health may be improved by intervening in an unfavourable lateral balance, such as via rTMS (Clow et al., 2003). Furthermore, it is possible that neuropsychological interventions could be devised and tested, to see whether they prevent or ameliorate the effects of chronic immune-related illnesses, as well as maintain good health in those unaffected by disease, particularly in people with poor left-HL. In a diagnostic setting, these findings could prove pertinent. Many chronic and life-limiting illnesses, such as HIV, show a vast range of individual differences in subjective symptomatic experience and prognosis (Balbin *et al.*, 1999; Grant & De Cock, 2001; Mindel & Tenant-Flowers, 2001), which could be explained, at least in part, by laterality effects. Moreover, research into this area of neuroimmunology could potentially allow us to understand more about the division of labour between the two hemispheres of the brain, particularly after trauma. From

studies that have examined hemispheric trauma (ie. epilepsy surgery or stroke) we can see the relationship between right hemisphere functioning (caused by left sided trauma) and poorer immunity. However, it is not clear whether this is caused by the effects of right-sided superiority, or left-sided inferiority. IHI can explain how HL influences immunity in this dichotic manner, but more research is required in order to understand its dynamics in this setting. In order to understand the clinical implications of laterality effects, investigation into which hemisphere exerts the most influence on immunity could be of vital importance, particularly given the suggestion by Lewis *et al.* (2007) that laterality can be essentially switched in certain psychological states. Finally, could HL also partly explain variability in the effectiveness of vaccines?

Tables

Table 1. Overview of studies on the relationship between hemispheric lateralisation and immune function

Table 2. Table of effect sizes for the main effects of the reviewed research

Figures

Figure 1. Quality assessment criteria

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Table 1. Overview of studies on the relationship between hemispheric lateralisation and immune function

Paper	Sample	Brain Measures	Immune Measures	Design	Results	Quality Score 0-17
Kang *et al*. 1991	20 (11 extreme stable right activation; 100% f, 17-20 years) Right handed in top or bottom 25th percentile of activation asymmetry.	EEG Also state-trait anxiety scale, BDI and Derogatis Stress Profile.	NK, lymphocyte proliferation (ConA, PHA, PW), T cell subset, plasma immunoglobulins and plasma cortisol. Also self-made questionnaire detailing frequency of common illnesses in preceding 2 and 12 months, family history of autoimmune diseases.	Cross-sectional	Lower levels of NKCA and IgM found in s' with frontal right activation as opposed to left. – not extended to T cell subset profile or lymphocyte proliferative response to ConA or PW. Proliferation to PHA was in the same direction as NKCA. Magnitude of difference in NKCA across both L and R groups was similar to the magnitude of difference in NKCA in stressful events. Immune patterns not accounted for by health survey, plasma cortisol levels, anxiety or depression.	9
Tarkowski *et al*. 1995	80 (51.25% f) stroke patients.	Hachinski method of assessing minor, major or progressive stroke. Lateralisation of stroke assessed by physical exam and CT scan.	Tuberculin for skin reaction. Histamine injection for T-cell mediated immune response. Axon reflex vasodilation. Stimulation of PBMCs to PPD, PHA and ConA to yield production of IFN-γ.	Quasi-experimental	Lateralisation of DTH response dependent on stroke clinical categorisation, motor function and side of lesion. Those with lesion on the right side had significantly larger DTH responses than those with left lesions which is independent of clinical categorisation of stroke.	7

Paper	Sample	Brain Measures	Immune Measures	Design	Results	Quality Score 0-17
Gruzelier *et al.* 1996	36 (27 with longitudinal assessments) asymptomatic HIV-1 infected patients, 100% male, 11.1% non-dextral.	EEG, WRMT, controlled verbal fluency, semantic processing test, finger tapping, grooved peg-board test, HADS, POMS.	CD4 and CD8 taken at study onset and at 6 month intervals for 30 months.	Cross-sectional	Superior left hemisphere functioning associated with higher CD4 count at baseline and through to study end. No relationship found between EEG activation asymmetry and CD4 count. Superior right functioning in WRMT indicated increased immune suppression (CD8). Higher POMS at onset predictive of poorer immune outcomes throughout study.	7
Tarkowski *et al.* 1998	117 in total split into 3 groups: 1) 44 early stroke patients (47.8% f, 23-81yrs) 2) 24 early stroke with retest (45.8% f, 23-76yrs) 3) 49 chronic stroke (40.8% f, 23-88yrs)	Hachinski method of assessing minor, major or progressive stroke. Lateralisation of stroke assessed by physical exam and CT scan.	Tuberculin for skin reaction. Histamine injection for T-cell mediated immune response. Axon reflex vasodilation. Stimulation of PBMCs to PPD, PHA and ConA to yield production of IFN-γ.	Quasi-experimental	Replicated former findings that DTH responses stronger in patients with right localised ischemic trauma, but also that those with right side trauma showed significantly different effects with time. The later challenges created greater immune effects on the paretic side later in the post-stroke period compared to those in the earlier challenges.	6
Davidson *et al.* 1999	24 healthy s', 37.5% female, 17-21 years	EEG Separately validated emotion eliciting film clips.	NKCA approximately 4 weeks after EEG data taken.	Experimental	Superior anterior left sided activation predicted higher NKCA (mid-frontal, lateral frontal and anterior temporal regions). Differences in posterior activation unrelated to NKCA measures. Lateral prefrontal activation asymmetry accounted for 21% of the variance in NKCA at final exam time, even when accounted for by baseline measures. S' with greater left frontal activation showed higher levels of NKCA after the positive film clip, this was exceeded by final exam effects which were three times greater.	10

Paper	Sample	Brain Measures	Immune Measures	Design	Results	Quality Score 0-17
Meador *et al.* 1999	11 surgical epilepsy patients: 20-48 years; 18.1% f; 8 R handed with L language dominance, 1 ambidextrous with L language dominance, 1 R handed with bilateral language representation (excluded from statistical analysis), 1 L handed with R language dominance (R temporal resection). 5 right, 5 left temporal lobectomies, 1 left frontal lobe resection.	Clinical diagnosis of epilepsy location and language lateralisation (language dominant resection = DOM; language non-dominant resection = NDOM).	Complete Blood Count (CBC): Total White Blood Cells (WBCs) Total $CD3^+$ $CD3^+4^+$ $CD3^+8^+$ $CD8^+$ Total lymphocytes Blood taken the day before surgery and a mean of 6 days after surgery.	Quasi-experimental	No significant main effects found aside from an elevation in WBCs in pre- to postoperative states across all patients. Interactions for DOM and NDOM groups for pre-/postop states were found for absolute lymphocyte, $CD3^+4^+$, $CD3^+8^+$, and total $CD8^+$. Follow-up contrast *t* tests performed showed significant results for increase in WBCs and decline in $CD8^+$ for the DOM group. The NDOM group showed significant increase in $CD3^+4^+$. All other *t* tests for the DOM group were non-significant, but were in the trend of the non-significant main effects; absolute lymphocyte decline, $CD3^+4^+$ decline, $CD3^+8^+$ decline, and total $CD8^+$ decline. The pre- and postoperative changes were in opposite directions for NDOM (increase) and DOM (decline) groups, aside for WBCs which were universal increase.	8
Ivashkova *et al.* 2002	Clinical group – 38 subacute stage stroke patients receiving TMS, 44-64yrs, 52.6% right hemisphere location. Control group – 30 healthy Reference group – 35 subacute stage stroke patients not receiving TMS, 54.3% right hemisphere.	None mentioned aside from stroke assessment.	CD3+, CD4+, CD8+ and CD22+ BTR of human leukocytes (ConA, PHA, PW) Lymphocyte suppressor activity Phagocytic activity of neutrophils (NTR) Leukocyte adhesion suppression.	Quasi-experimental	The type and degree of immune alterations was dependent on the lateral location of the lesion. Right hemispheric stroke resulted in $CD3^+$ and $CD8^+$ decrease, and $CD4^+/CD8^+$ ratio increase and disturbances in lymphocyte proliferation activity compared to healthy controls. Left hemispheric stroke resulted in $CD3^+$, $CD4^+$ and $CD8^+$ decrease as well as disturbances to lymphocyte proliferative activity in comparison to healthy controls. TMS of sensory and motor regions of the cortex of right hemispheric stroke patients caused normalisation of immune values. Change less pronounced after TMS for left hemispheric patients.	8

Paper	Sample	Brain Measures	Immune Measures	Design	Results	Quality Score 0-17
Clow *et al.* 2003	16 healthy participants, 37.5% f. Two males and one female studied twice.	TMS to both hemispheres separately.	Salivary S-IgA and salivary volume.	Experimental	TMS to the left hemisphere causes upregulation of S-IgA. TMS to the right causes reduction in saliva volume. S-IgA rises after TMS on both sides but with salivary volume falling there is a significant increase after left TMS rather than right.	8
Dziedzic *et al.* 2003	Reference Group – 26 right handed stroke patients; 11 right lesion (45.5% f; mean age 63.7); 15 left lesion (46.7% f; mean age 60.6). Control group – 16 healthy s' (43.8% f, mean age 62.3).	Stroke location and size determined by CT scans.	Serum IL-10 and IL-6.	Cross-sectional	Both left and right stroke patients had significantly higher levels of IL-10 and IL-6 than healthy controls. IL-10 was higher in left stroke patients and there was no difference in IL-6 in either patient group.	9
Meador *et al.* 2004	22 surgical epilepsy patients; 19-61 years, 45.5% f, 81.8% left language dominant (others mixed), half right resection half left. Healthy controls.	None mentioned aside from clinical diagnosis. POMS and daily stress inventory taken.	CBC Lymphocyte subset analyses Mitogen and microbial responses Histamine skin testing Cortisol	Quasi-experimental	Lymphocytes, total T cells, cytotoxic T cells and T helper cells decreased with left and increased with right resections; these effects were unaltered when mood and cortisol accounted for. No differences in mitogen and microbial responses. Greater right arm histamine wheal responses found in left-brain dysfunction as compared to right and control. Histamine flare responses decreased after left resection and increased in right resection patients as compared to right sided patients and controls.The four patients with atypical language lateralisation had left lesions and surgery, cellular and skin responses differed from left resection patients with normal language lateralisation.	7

Paper	Sample	Brain Measures	Immune Measures	Design	Results	Quality Score 0-17
Koch *et al.* 2006	56 acute stroke patients (11 TIA, 17 Lacunar, 20 atherothrombotic, 8 cardio-embolic). Mean age 58.9, 46.4% female, 31 left localisation of stroke, 25 right localisation.	MRI/CT for localisation of stroke trauma.	C-Reactive Protein (CRP) and WBC (retrospective collection from medical notes)	Quasi-experimental	Left hemispheric stroke resulted in increased variability in CRP and WBC, and higher absolute values of CRP and WBC. Correlation between CRP and WBC only observable in left-sided stroke patients.	8

Table 2. Table of effect sizes for the main effects of the reviewed research

Paper	Effect	Effect Size (*r*)	Mean *r* for the Study
Kang *et al.*, 1991	Natural Killer Cell Activity (NKCA) – Left vs Right – overall	0.678	
	Lytic Units at 30%	0.559	
	IgM – Left vs Right	0.527	0.588
Wittling & Schweiger, 1993	Cortisol Secretion (CS) - "Low" physical complaints – Left vs Right film presentation	0.916	
	CS – "High" physical complaints – Left vs Right film presentation	0.711	0.814
Tarkowski *et al.*, 1995	Lateralisation of stroke-induced lesion & DTH – Left vs Right	0.280	0.280
Gruzelier *et al.*, 1996	Word fluency (Left) and CD4	0.610	
	Semantic processing errors (Left) and CD4	0.480	
	Finger tapping asymmetry (dominant hand) and CD4	0.540	
	Memory for faces (Right) and CD8	0.530	0.540
Tarkowski *et al.*, 1998	Early stroke & DTH – Left vs Right	0.862	
	Right subcortical lesions & DTH – Paretic vs Contralateral	0.675	0.769
Davidson *et al.*, 1999	Baseline frontal asymmetry & baseline NKCA (11:1 ratio)	0.460	
	Baseline frontal asymmetry & baseline NKCA (33:1 ratio)	0.510	
	Baseline lateral frontal activation & baseline NKCA (11:1 ratio)	0.410	
	Baseline anterior temporal activation & baseline NKCA (11:1 ratio)	0.480	
	Baseline anterior asymmetry & NK reactivity to emotional film clips	0.440	0.460
Meador *et al.*, 1999	DOM vs NDOM group – Pre- to Post-op – Absolute Lymphocytes	0.647	
	DOM vs NDOM group – Pre- to Post-op – Total $CD3^+$	0.675	
	DOM vs NDOM group – Pre- to Post-op – $CD3^+CD4^+$	0.666	
	DOM vs NDOM group – Pre- to Post-op – $CD3^+CD8^+$	0.675	
	DOM vs NDOM group – Pre- to Post-op – $CD8^+$	0.678	0.669

Ivashkova *et al.*, 2002*	Right vs Left hemispheric stroke pre-TMS – cellular immunity (mean value)	0.794	
	Right vs Left hemispheric stroke pre-TMS – neutrophil activity (mean value)	0.938	0.866
Clow *et al.*, 2003		Not Available	
Dziedzic *et al.*, 2003		Not Available	
Meador *et al.*, 2004	Lymphocytes – Left vs Right across Pre/Post operative	0.535	
	Total T cells – Left vs Right across Pre/Post operative	0.587	
	Helper T cells – Left vs Right across Pre/Post operative	0.587	
	$CD3^{+}8^{+}$ – Left vs Right across Pre/Post operative	0.494	0.551
Koch *et al.*, 2006	C-Reactive Protein level – Left vs Right	0.125	
	White Blood Cell level – Left vs Right	0.196	0.161

Effect Size (*r*) designations (Cohen, 1988)
Small = 0.1
Medium = 0.3
Large = 0.5

* This study involved multiple interactions between 11 immune parameters (5 cellular immunity, 6 neutrophil activity) and four interactions (Left vs Right; Pre TMS vs Post TMS; Control vs Left and Right – Pre TMS; Right Pre & Post vs Left Pre & Post). To avoid reporting all 77 calculated effect sizes, the mean effect size of all of those in that section (T cell or lymphocyte proliferation) was used to illustrate the main lateralisation finding of the study.

Figure 1. Quality Assessment Criteria

1) Design (scoring 0-2)

0= cross-sectional
1= quasi-experimental (eg. using clinical groups as "experimental" conditions)
2= experimental
An additional point is offered if the results are compared between two or more groups

2) Sample (scoring 0-2)

0= small (<40)
1= moderate (40-79)
2= large (80+)

3) Third Variables (scoring 0-5)

0= none considered
1= a total of 1 or 2 (from one or more groups) (see below)
2= a total of 2-4 (from one group)
3= a total of 2-4 (from two or more groups)
4= a total of 4+ (from one group)
5= a total of 4+ (from two or more groups)

Groups:

- Psychological – Anxiety/depression, current mood, life events, family, sexuality, employment status and type, IQ.
- Physiological – Comorbid illness, medications, activity/lifestyle, prior dependence of drugs/alcohol, current use of nicotine and caffeine.
- Neurological – ANS interactions, handedness, language lateralisation, previous TBI or neurological disorder.
- Background – SES, age, education, gender.

4) Statistics (scoring 0-4)

0= 0/4 suitability criteria
1= 1/4
2= 2/4
3= 3/4
4= 4/4

Criteria:

- Appropriate choice (parametric assumptions, degrees of freedom, prospective power analyses, bivariate vs multivariate, data transformations)
- Control for third variables (baseline adjustments, missing data, sphericity adjustments etc.)
- Setting of *p* value to .01
- Post-hoc analyses (further stat testing, power analyses, mediating/moderating effects, prospective assessment for further testing if applicable)

5) Conclusions (scoring 0-4)

0= 0/4 suitability criteria
1= 1/4
2= 2/4
3= 3/4
4=4/4

Criteria:

- Conclusion validity
- Limitations
- Contextual evaluation
- Indications for future research