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Hemispheric Lateralisation and Immune Function: A Systematic Review of Human Research

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Abstract

Past studies examined relationships between hemispheric lateralisation (HL) and immune system functioning. 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 $r = 0.536$ (range 0.280-0.866). Collectively, studies point at left-HL and stronger immunity relationships. Limitations, mechanisms and clinical implications are discussed.

Keywords: Hemispheric Lateralisation; Immune Function; Neuroimmunology; 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; Tracey, 2002; 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 achieved via autonomic 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 also been described (Bellinger *et al.* 2006; 2008; Quan & Banks, 2007; Tracey, 2002; 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 – Hemispheric 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 activationally or functionally dominant 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; Sackeim *et al.*, 1984; Wittling *et al.*, 1998). 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, a study using rats with implanted electrical cortical 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 termed this "anomalous dominance" (ie. right sided "abnormal" language lateralisation). Observing higher incidences of left-handedness amongst individuals with developmental and immune disorders, they 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 effects of HL 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. Handedness is only one of many activities and behaviours that are lateralised and cannot comprise a total asymmetry index (McManus & Bryden, 1991). Furthermore, handedness is very poorly correlated with HL, but rather may be indicative of language lateralisation only, as language lateralisation in sinistrals is heterogeneous, whereas with dextrals it is almost exclusively in the left hemisphere (Gruzelier *et al.*,

1996; Jung *et al.*, 2003; Knecht *et al.*, 2000; Toga & Thompson, 2003). Moreover, a study using mice showed that handedness effects on immunity were abolished with left, but not right, cortical ablation (Neveu *et al.*, 1991), suggesting the involvement of more complex brain organisation factors in the HL-immunity relationships. While handedness is related to hemispheric specialisation (e.g., left hemisphere specialising 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. Below we provide a more comprehensive definition of HL.

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 in humans, nor do we know the magnitude of such a relationship. This could be, at least in part, due to the fact that laterality itself is difficult to define – with the term being mostly applied to cognitive attributes. The present review aims to synthesize the currently available research, assess its methodological quality and effect sizes, delineate study limitations, and interpret the findings with a view to future advancements in the research area and its clinical implications.

Definition of Hemispheric Lateralisation in Neuroimmunology

For the purposes of this review, the definition of HL for neuroimmunology should be separated from that used in cognitive neuroscience. The latter uses HL in the context of *hemispheric specialisation,* whereas the broader concept of *hemispheric activation* is the basis for this area of neuroimmune theory. It has been suggested that hemispheric activation can actually influence hemispheric specialisation (Davidson *et al.*, 1999; Davidson & Hugdahl, 1996; Kang *et al.*¸1991), which means that focusing on the cognitive terms of specialisation alone may not reflect the true antecedents of the immunological influence. Moreover, activation can be independent of hemispheric specialisation (Davidson & Hugdahl, 1996).

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

Selection of studies was based upon their relevance to humans, and their relevance to relationships between lateralisation and aspects of immune functions, using either a cross-sectional or experimental design. Studies that did not primarily assess this relationship were also considered if their data examined this as a secondary analysis. This systematic review was limited to papers published in English or French. Studies that were excluded include those not employing functional or activational assessments of laterality (such as handedness), and those using clinical conditions that resulted in more complications than just lateralisation (eg. cerebral palsy). Studies that did not employ direct immunological measures as an outcome measure (ie. self-report health surveys) were excluded.

Quality Assessment

In the absence of a standardised checklist for such heterogeneous data, a quality assessment scale was developed from quality assessment frames such as can be found in Mols *et al*. (2005) and Borghouts *et al.* (1998). 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 (see figure 1). 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

Summary of extracted details from the studies included: research team, year of publication, sample details, types of HL and immunological tests, research design and 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 information relevant to the statistical tests used for each main relationship or effect studied. Mean effect sizes across study type (cross-sectional, semi-experimental) and across all studies were calculated to yield a single scale for comparison across studies. This procedure was again employed to assess across groups of activation and functional analysis.

3. Results

Study Characteristics

After all exclusion criteria were applied to the identified literature, 11 articles were 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

To assess inter-rater reliability of quality assessment, scores were correlated using simple bivariate correlation with SPSS. 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 inferential 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, five of the nine studies (67%) had large mean effect sizes for their main effects; two 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 0.532, 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 0.533. 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 0.537. 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.

Each study was also classified as to whether HL was measured according to activity or function. Studies including patients after stroke or epilepsy, using EEG or brain stimulation, were classified into the activity HL group. Studies using neuropsychological tests or linguistic dominance were classified into the functional HL group. It is important to note that this classification is not perfect since lesions due to stroke or epilepsy could be construed as both reflecting changes in activity and

function. Nevertheless, we related them to the activity group since changes following stroke, for example, are marked first by reductions in neuronal activity (Zhang et al., 2010). We then classified studies into activity versus functional measures of HL, since the studies utilized either or both types. Functional measures (2 studies alone) yielded an effect size of 0.63 while activity measures (8 studies) yielded an effect size of 0.515.

Quasi-Experimental and Experimental Data

The studies in this group 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 (n=24) displayed smaller delayed type hypersensitivity (DTH) responses than those with right lesions (n=26), 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 undertaken (e.g., age, hypertension, medications), 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 conducted either, limiting the inferential validity of the findings. It should also be noted that allergic responses in the skin can also be influenced by handedness (Bryden, Bruyn & Fletcher, 2005); which could have implications for the interpretation of the present findings.
Classification: Activity

Tarkowski et al., 1998

In a follow-up study, Tarkowski *et al.* (1995) employed the same methodology, but divided the clinical sample of stroke patients 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 the early stroke group with localised right trauma exhibited larger DTH responses to immune challenges. This was observed in both the paretic and contralateral sides in comparison 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 study also considered a substantial number of third variables, although there were no controls for levels of depression, anxiety or general mood, which are related to immune function (Kemeny & Schedlowski, 2007), and are clinically relevant in such patient samples.
Classification: Activity

Davidson et al. 1999

In a sample of healthy students Davidson *et al.* (1999) used emotionally evocative film clips to manipulate natural killer cell activity (NKCA) in left and right lateralised participants, as determined by electroencephalography (EEG). 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 had 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 generalisable to various contexts.

Classification: Activity

Meador et al., 1999

Including 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, in relation to several immunological outcomes. Resection surgery is employed with intractable epilepsy, whereby an area of the affected lobe is excised in order to diminish the epileptogenic activity. 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 total WBC counts, 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 number of *post-hoc* tests were employed, although it is not clear whether statistical adjustments were made for these multiple comparisons. However, the overall observed trend 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). Whilst the use of the DOM/NDOM classification is useful to partly understand the HL of the patients; looking at resections in these categories as opposed to absolute left/right hemispheres, is conceptually problematic as it defines laterality in relation to function or specialisation, rather than to activity and side. It is known for example that not all individuals have a left side language dominance.

Classification: function & activity

Ivashkova et al., 2002

Ivashkova *et al.* (2002) used three groups of participants; a group of subacute stage stroke patients who received transcranial-electromagnetic stimulation (TeMS) therapy; a reference group of subacute staged stroke patients who did not receive 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. 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 finding of the study was that lateral localisation of the lesion was directly involved in the type and degree of observed immune alteration. The main limitation of this study is the disparity between study groups, making comparison between these groups more circumspect. The control group (n=30) was compared against two clinical groups (total n=73); and the TeMS and non-TeMS groups were equally disproportionate (n= 68, 35 respectively). Methodologically, the study is also limited by the use of multiple statistical tests, risking a type 1 error, without employing an appropriate correction. They report performing an extremely large number of t-tests (77), and if the standard Bonferoni correction for multiple comparisons, dividing the p critical value (0.05) by the number of t-tests (77), were applied it is unlikely that many (if any) of the results would survive. However, the use of a control group and a reference group 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. *Classification: Activity*

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 Immunoglobulin 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 rTMS and HL on immunity.

Classification: Activity

Meador et al., 2004

This research group again used surgical epilepsy patients to examine post-surgical changes in immune parameters. This study also used analyses of the same variables in a healthy control sample to control for variability in these measures. 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 location 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, suggesting that mood is not a moderator in the relationship. 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 previous Meador *et al.* (1999) study, 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 and more coherent. The use of cellular proliferation tests 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). Further research is required to expand upon the different immunological consequences of left HL. Nevertheless, concerning only the lymphocyte data, these results are in line with a differential (and inverse) immunological function of HL.
Classification: Activity

Koch et al., 2006

In the more recent of the reviewed studies, Koch *et al.* (2006) also 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, interpreted by the investigators as suggesting a deficit in immune control after left-sided ischemia. This study limited its examination to the immune parameters of WBC and CRP, which limits the comparison to similar studies under review here (eg. Meador *et al.*, 2004) due to the non-specificity of such markers. Furthermore, the immune measures were only conducted in the first 24 hours since 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. This is in stark contrast to the methods employed by the Tarkowski work groups (Tarkowski *et al.*, 1995; 1998); who assessed immune alterations longitudinally across the course of stroke clinical staging. In addition, no theoretical rationale for examining the relationship between CRP and WBC was provided. Does a greater variability in these two immune measures exist among left-hemisphere people, or does the left hemisphere in general regulate one or both parameters, possibly influencing the other one? Finally, what does lack of a correlation between CRP and WBC mean biologically? Thus, beyond methodological limitations, the interpretation and meaning of the observed results remain problematic.

Classification: Activity

Cross-Sectional or Prospective Data

Three studies involved using healthy (Kang *et al.*, 1991) and clinical (Dziedzic *et al.*, 2003; Gruzelier *et al.*, 1996) participants; and 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"; designated as those in the upper and lower quartile of prefrontal activation asymmetry. 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 may raise 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. However, 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). The observed 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.

Classification: Activity

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 was not and 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, reviewed here, the Gruzelier *et al.* (1996) study shows a prospective relationship between two different measures of HL, function and activity, with immunity in the context of an immune-related illness. However, to ensure these findings are valid, future studies must replicate it and address its many limitations.

Classification – activity & function

Dziedzic et al., 2003

This study used stroke patients to examine the relationship between stroke location and interleukin (IL)-10, and IL-6. Stroke location and size were assessed using CT scans. An age- and gender-matched control group was used to compare general immunological parameters, but were not assessed for any form of lateralisation and so were not included in the analysis of the main effect. 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 including cytokines which clearly reflect cellular immunity activity (e.g., Interferon-gamma) 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.

Classification - Activity

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 (27.3%) studies describe 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 (27.3%) studies describe 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 (45.4%) studies describe 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 a trend that HL, as a neuropsychological phenomenon, plays a key role in the functioning of the immune system in both health and sickness. However, the critical methodological limitations of this set of studies necessitates caution; and it is immediately apparent that research in to this relationship should be conducted with more control for confounding variables before any resolute conclusions can be ascertained. Importantly, the findings

reviewed here suggest one direction; namely that the left hemisphere is immunopotentiating, the right is immunosuppressing. Although the mechanisms of this directionality cannot be ascertained by current knowledge; one possibility is by means of interhemispheric inhibition (IHI). IHI is thought to mainly take place via the corpus callosum (Geffen *et al.*, 1994; Sullivan, 2004), and could explain the changes in immunoregulation following cerebral trauma such as stroke or surgery.

The mean effect size (r=0.536) for the HL-immune relationship determined on the basis of the studies included here was large. Two of the nine studies studies reported mean effects in the upper quartile (r>0.65) (Ivashkova *et al.*, 2002; Tarkowski *et al.*, 1998). These studies were both from the quasi-experimental/experimental category, which provides some encouragement for this relationship in the context of the many methodological flaws of this study set. The mean effect size (r=0.503) 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 (r=0.374) for the studies observing the opposite relationship (Dziedzic *et al.*, 2003; Kang *et al.*, 1991; Koch *et al.*, 2006). We then classified studies into activity versus functional measures of HL. Functional measures (2 studies alone) yielded an effect size of 0.63 while activity measures (8 studies) yielded an effect size of 0.515. 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 – and so these must be viewed with caution. Thus, we chose to focus on overall effect sizes, which can provide a standardised means of elucidating combined findings, by providing a combined perspective of the data. The fact that 55% of the effect sizes showed "large" effect sizes in the same direction is perhaps the most promising finding of the combined results, however it should be noted that many of the studies had small sample sizes – a factor which is known to increase effect size (Givens *et al.*, 1997). This indicates that despite the differences in methodology, the relationship between left-HL and enhanced immunity can be observed even under less than ideal conditions.

Concerning quality assessment, there were three studies that received observed scores in the upper quartile (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 these more methodologically rigorous studies supported the conclusion that left-HL is related to immune potentiation. The mean quality assessment score (7.9) of all studies was under 50% of the 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. 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 does not appear to mediate or moderate the association between HL and immunity (Kang *et al.,* 1991; Meador *et al.,* 2004). This could mean 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 nervous system (SNS) since provision of beta-blockers reduced the HL-immune relationship in rats (Moshel et al., 2005). There are also suggestions that there is hemispheric specialisation in autonomic control of the heart in humans, with the right hemisphere exerting sympathetic control and the left parasympathetic (Wittling *et al.*, 1998). Future studies are needed to replicate and extend these findings, and must test the functional and health implications of such mediation.

Clinical implications

The study by Gruzelier *et al*. (1996), though with several limitations, shows that HL may be related to immunity in HIV. A more recent study found that right-HL predicted symptoms of upper respiratory tract infections, independent of multiple confounders (e.g., age, sex, IQ; Gidron *et al.*, 2010). Both studies 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 important implications to understanding neuroimmunomodulation of diseases and to opening new therapeutic approaches that need to be tested. 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 greater 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, whether related to cerebral HL or not, is 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. To the best of our knowledge, it is 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 lateralisation effects (nature, duration, development, 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 suggested differential immunomodulation by left versus right HL, could lateralisation predict the onset or prognosis of immune-related illness? The evidence from Gruzelier *et al. (*1996) and Gidron *et al.* (2010) indicate 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 widespread 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 increased right hemisphere activity and functioning and poorer immunity. However, it is not clear whether this is caused by the effects of right-sided superiority, or left-sided inferiority,

following a left-sided lesion. 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? One study has found that higher levels of left prefrontal activation were related to a more effective antibody response to influenza vaccination (Davidson, Kabat-Zinn, Schumacher, Rosenkranz *et al.*, 2003). Such questions remain to be addressed in the next decade of research on HL, immunity and immune-related diseases.

Tables

Figures

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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.	Intracarotid amobarbital test to assess language dominance. 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