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Altered functional neuronal activity in neuropsychiatric lupus: A systematic review of the fMRI investigations

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ABSTRACT

Objective: Recent years have seen a rapid increase in the investigation of neuropsychiatric lupus (NPSLE) through the use of functional magnetic resonance imaging (fMRI). Measuring specific neuronal activity in regional brain structures during a cognitive task may identify possible biomarker for NPSLE.
Methods: A systematic review of fMRI studies of systemic lupus erythematosus (SLE) is carried out to address common findings that characterize NPSLE.
Results: A disturbance to the working memory and executive function brain regions is among the most well-replicated finding. Differences in brain activation may relate to an early primary dysfunction of these regions. Increased functional connectivity strength in the fronto–parietal cortex in the resting state is correlated with SLE disease activity in one study. Decrease functional connectivity is observed in lupus patients with long-term disease. However, there is strong evidence that points toward a lack of effective integration of distributed functional brain regions and disruptions in the subtle modulation of brain function in relation to task demands in SLE. Limitations of the literature to date include the use of small sample size and the lack of addressing the effect of confounding variables, including immunosuppressive treatment.
Conclusion: Careful definitions of the fMRI technique used both in the design, analyses, and interpretation of high dimensional data is needed, when dealing with a limited number of SLE subjects with heterogeneous manifestations and unknown pathophysiology.

Introduction

Neuropsychiatric involvement (NPSLE) is the least understood manifestation of systemic lupus erythematosus (SLE) and is associated with widespread of clinical presentations [1]. NPSLE syndromes range from diffuse central nervous system (CNS) disorders (e.g., acute confusional state, psychosis, anxiety, and depressive disorders including cognitive dysfunction) to focal CNS syndromes (e.g., seizures, cerebrovascular disease, chorea, myelopathy, transverse myelitis, demyelinating syndrome, aseptic meningitis, and headaches), dysautonomia and peripheral nervous system disorders (e.g., neuropathies and acute inflammatory demyelination) [2].

Cognitive dysfunction is the most commonly encountered symptom of NPSLE, other than headache, with a prevalence rates ranging from 20% to 80%, largely depending on the methodological and diagnostic purposes. Cognition impairment in SLE can affect any or all of the following functions: simple or complex attention, reasoning, executive skills (e.g., planning, organizing, and sequencing), memory (e.g., learning and recall), visual–spatial processing, and language (e.g., verbal fluency), and psychomotor speed [2]. The severity of cognitive dysfunction in SLE ranges from mild impairment to severe dementia. Currently, formal neurocognitive testing is considered the criterion standard for diagnosing cognitive dysfunction in SLE [3]. Neuropsychological studies have identified many differences between individuals with SLE and healthy controls, in particular differences in sensory processing, disturbances in executive function and a reduced capacity to appreciate the mental states of others. Nonetheless, the etiology of this complication remains elusive and continues to be an active research question.

Neuroimaging is a potential mean to non-invasively assess brain pathology in NPSLE. Magnetic resonance imaging (MRI) has commonly revealed lesions in the brain tissue of individuals with NPSLE, but these findings have not been effective markers of active NPSLE, nor have they explained the specific cognitive changes encountered [4]. While evidence of cortical and subcortical neuropathology has been demonstrated in MRI studies using magnetization transfer imaging and fluid-attenuated inversion recovery [5,6], no clear association of these findings with clinical symptoms has emerged, that could be considered when making or evaluating treatment decisions. Likewise, limited insight into the patterns of

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cognitive deficit in patients with SLE has been provided with other imaging methods, such as magnetic resonance spectrometry [7], positron emission tomography (PET) [8,9], and single-photon emission computed tomography (SPECT) [10,11].

A major contributor to the increase in understanding of neuropsychiatric syndromes has been the development of functional magnetic resonance imaging (fMRI), a technique which exploits the differences in the ferromagnetic properties of oxygenated and deoxygenated blood to produce an indirect measure of neuronal activity [12]. Since its development, fMRI has been widely applied in individuals with different neuropsychiatric syndromes including SLE using a variety of populations (NPSLE and non-NPSLE), tasks, and methods of analysis. This review aims to characterize the SLE populations examined and the methodology used so that common findings from across studies can be identified.

Methods

Literature search methods

Medline, Embase, Scopus (Elsevier), and PsycINFO were searched for all English language studies, published between January 1984 and January 2015 that reported functional MRI data in patients with SLE. Search terms included "lupus," "neuropsychiatric syndrome," and "mental disorder"; related terms were combined using the AND operator with "functional magnetic resonance imaging" OR "fMRI." Both free-text and expanded medical subject headings were used. The search strategy was supplemented by using the reference lists of the included articles.

Inclusion criteria

Articles were included if they were primary research studies published as peer-reviewed articles in English and they compared a sample of participants with systemic lupus erythematosus with a group of controls, using fMRI.

Data extraction

For each study, data of the participant group were extracted: gender, mean age, and mean IQ. Where possible, data pertaining to the diagnosis of SLE was also extracted, including the diagnostic criteria used. The selection of the comparison group and features by which they were matched to the SLE group was also recorded. Details of the fMRI paradigm were also extracted and studies were grouped according to the element of cognition under investigation. The fMRI studies were allocated to specific task domains: motor tasks; visual processing tasks; executive function tasks; auditory and language tasks; basic social processing tasks (face processing, emotion processing, and eye gaze); and complex social cognition tasks (irony comprehension and empathy).

Results

Included papers

Overall, 10 articles [13–22] were identified which reported using fMRI paradigms to investigate NPSLE. One article [14] did not include a healthy control group but has compared early onset of disease (<2 years duration) with late onset of disease (>10 years duration). All the articles included adult SLE patients, while 2 articles included children with SLE [17,19]. The Figure describes the flow chart of the literature search.

Details of SLE participants

A summary of the studies [13–22] is depicted in the Table. The largest original study consisted of 31 participants with SLE,

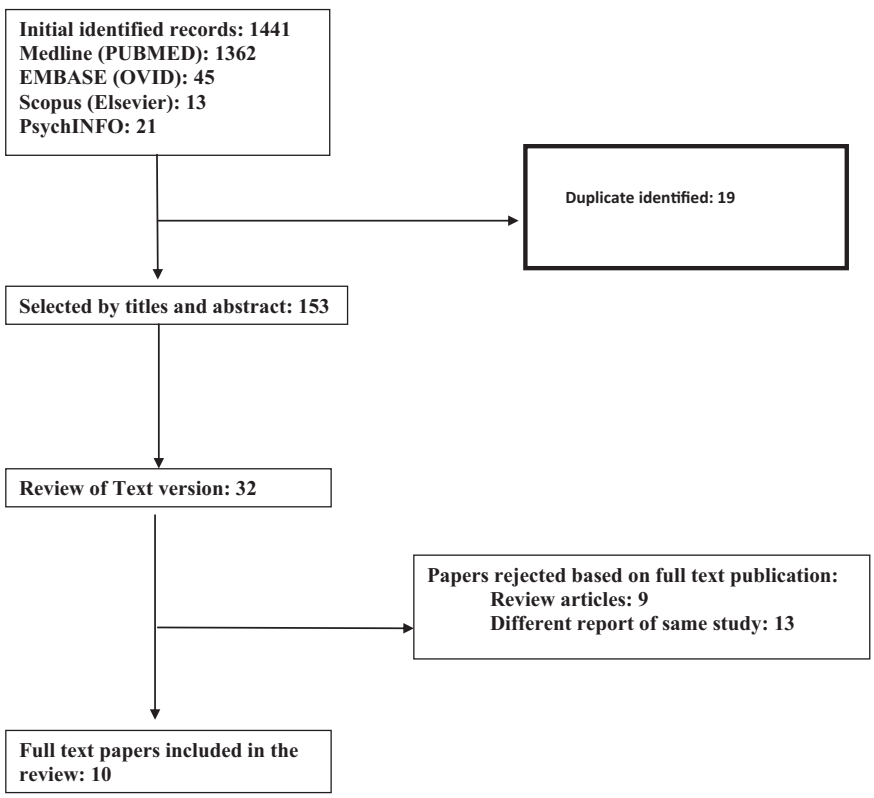

Fig. Flow of study selection.