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Altered likelihood of brain activation in attention and working memory networks in patients with multiple sclerosis: An ALE meta-analysis☆

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ABSTRACT

Multiple sclerosis (MS) is a chronic neurological disease, frequently affecting attention and working memory functions. Functional imaging studies investigating those functions in MS patients are hard to compare, as they include heterogeneous patient groups and use different paradigms for cognitive testing. The aim of this study was to investigate alterations in neuronal activation between MS patients and healthy controls performing attention and working memory tasks. Two meta-analyses of previously published fMRI studies investigating attention and working memory were conducted for MS patients and healthy controls, respectively. Resulting maps were contrasted to compare brain activation in patients and healthy controls. Significantly increased brain activation in the inferior parietal lobule and the dorsolateral prefrontal cortex was detected for healthy controls. In contrast, higher neuronal activation in MS patients was obtained in the left ventrolateral prefrontal cortex and the right premotor area. With this meta-analytic approach previous results of investigations examining cognitive function using fMRI are summarized and compared. Therefore a more general view on cognitive dysfunction in this heterogeneous disease is enabled.

Contents

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1. Introduction

Multiple Sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system (CNS) characterized predominantly by demyelinating lesions in the white matter of the brain and the spinal cord. Conventional structural magnetic resonance imaging (MRI) can be used to identify and quantify these lesions. Furthermore, focal demyelination and neuronal loss of gray matter, appearing as partly or entirely cortically located lesions on MRI images as well as structural damage of white and gray matter appearing normal on conventional MRI images are components of the disease (Lassmann, 2008). A hallmark of CNS lesions characteristic for MS is disseminations in both space and time. Due to spatially disseminated damage to the CNS, MS results in a wide spectrum of clinical manifestations ranging from motor symptoms to cognitive and neuropsychiatric deficits. Disease onset peaks between 22 and 30 years and women are affected approximately twice as often as men (Alonso and Hernán, 2008).

The different clinical courses of MS can be categorized into four types based on disease progression (Lublin and Reingold, 1996): Relapsing-remitting MS (RRMS) which is characterized by clearly defined relapses with full recovery or sequelae and residual defects. During periods between relapses the disease does not progress clinically. In case this phenotype of the disease is followed by a progression with or without occasional relapses, minor remissions, and plateaus it is classified as secondary progressive MS (SPMS). In contrast, primary progressive MS (PPMS) takes a progressive course from the beginning with plateaus and temporary minor improvements. The fourth type is progressive-relapsing MS (PRMS), which is progressive from the onset with acute relapses. Between the relapses there is continuing progression. Superimposed relapses may occur in SPMS, whereas in PPMS no acute relapses occur (patients with relapses are then categorized as having PRMS; Lublin and Reingold, 1996).

Among the clinical symptoms which affect all types of MS cognitive impairment is the most common symptom with prevalence rates between 43% and 70% significantly contributing to the extent of disability (Benedict et al., 2006; Peyser et al., 1990; Rao et al., 1991). Memory, attention, processing speed, information processing efficiency, and executive functioning have been shown to be the cognitive capacities that are most frequently impaired (Benedict et al., 2006; Rao et al., 1991).

Functional MRI (fMRI) has been used to identify brain regions that are on the one hand involved in cognitive functioning in healthy individuals and on the other hand showing altered activation in MS. FMRI studies that explored cognitive processes in MS examined a great variety of functions, such as working memory, attention, and executive functions (Chiaravalloti and DeLuca, 2008) using paradigms such as the Paced Auditory Serial Addition Test (PASAT; e.g. Audoin et al., 2005; Forn et al., 2006; Mainero et al., 2004), the Paced Visual Serial Addition Test (PVSAT; Bonzano et al., 2009), and the n-Back task (e.g. Amann et al., 2011; Cader et al., 2006; Forn et al., 2007; Sweet et al., 2004). These abilities were not only examined in behavioral studies, but also using functional imaging to explore the neuronal correlates of impaired performance.

During the last years, the number of functional imaging studies rapidly increased as the neuroscience community urged to gain more detailed insight into diseases progression and prognosis, as well as therapeutic options. However, results of these studies are hardly comparable, as typically stimulation paradigms, disease phenotypes, and statistical evaluation of fMRI data show huge variability. Therefore, the current study aimed at providing an overview of previous literature in conjunction with the mapping of functional brain activity related to attention and working memory function in MS patients with high statistical probability performing meta-analyses in order to present a comparison of neuronal activity patterns of MS patients with those of healthy controls.

2. Materials and methods

2.1. Study selection

For this meta-analysis peer-reviewed studies on functional neuroimaging of attention and working memory processes in patients with multiple sclerosis, published in the English language between 1996 and February 2013 were identified.

Literature research was performed using PubMed, an online database including more than 22 million citations for biomedical literature using the following keywords: *functional MRI*; *positron emission tomography*; *multiple sclerosis* (including common abbreviations like *fMRI*, *PET*, and *MS*); which were cross-referenced with the search terms *cognition*; *information processing speed*; *memory*; *working memory*; *executive functions*; *selective; focused or sustained attention*; and *attention*. In addition, we used search terms for tasks associated with working memory and attention like n-Back; *Paced Auditory Serial Addition Test*; and *Paced Visual Serial Addition Test* (including the common acronyms PASAT and PVSAT) as cross-reference. In a second step, the reference lists of the original articles resulting from this search were examined in order to find additional publications that were not identified by the database search.

For the current meta-analysis the following seven inclusion criteria were specified:

1. Studies must include patients with diagnosed multiple sclerosis, studies including patients with Clinically Isolated Syndrome (CIS) with the diagnosis “possible MS” were excluded.
2. Included studies had to focus on attention and working memory processes by using auditory or visually presented stimuli. Studies, that used cognitive paradigms investigating attention in conjunction with higher cognitive abilities, such as response inhibition, were excluded.
3. The studies had to examine neuronal activity in working memory and/or attention tasks with means of functional magnetic resonance imaging (fMRI) or positron emission tomography (PET).
4. As contrasts used for fMRI or PET analysis we only included direct comparisons between attention or working memory task against a baseline condition for MS patients and healthy controls separately. Comparisons between healthy controls and MS patients without reporting brain activation for each group separately were not included.
5. Only studies reporting coordinates of a whole-brain analysis for patients and healthy controls separately were included. Studies reporting only results of regions of interest (ROI) analyses, volume of interest (VOI) analyses, or small volume correction (SVC) were excluded. Also, studies that reported only correlations of BOLD signal changes with respect to other measures were excluded.
6. All reported results had to be corrected for multiple testing at a significance level of $p < 0.05$, uncorrected data had to be thresholded at $p < 0.005$.
7. Included coordinates had to be reported in either standard Talairach space or the Montreal Neurologic Institute (MNI) space.

2.2. Activation likelihood estimation

Activation likelihood estimation (ALE) meta-analyses (Turkeltaub et al., 2002, 2012; Laird et al., 2005; Eickhoff et al., 2012), were performed using GingerALE 2.1 (www.brainmap.org/ale). If necessary, neuroanatomical coordinates reported in MNI space were transformed to Talairach