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# Effects of fatigue on cognitive control in neurosarcoidosis

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**Abstract**
Fatigue is a usual reaction to prolonged performance but also a major symptom in various neuroimmunological diseases. In neurosarcoidosis fatigue is a core symptom, but little is known about the relevance of fatigue on cognitive functions in this disease. Previous results in healthy subjects suggest that fatigue strongly affects cognitive control processes. However, fatigue is not a uni-dimensional construct but consists of different facets. It is unknown which of these facets are most important for mechanisms of cognitive control. In the current study we investigate conflict monitoring and response selection processes in neurosarcoidosis patients as a 'model disease' of fatigue and healthy controls in relation to the impact of 'cognitive' and 'motor fatigue' on these processes using event-related potentials (ERPs). We focus on ERPs reflecting attentional selection (P1, N1) and conflict monitoring/response selection processes (N2). ERPs reflecting attentional selection processes were unchanged. The N2 on incompatible trials was reduced in neurosarcoidosis suggesting that response selection and conflict monitoring functions are dysfunctional. Of note, fatigue strongly modulates responses selection processes in conflicting situations (N2) in controls and neurosarcoidosis, but the effect of fatigue on these processes was stronger in neurosarcoidosis. Neuroimmunological parameters like TNF-$\alpha$ and soluble interleukin-2 receptor serum concentrations do not seem to modulate the pattern of results. Concerning fatigue it seems to be the 'cognitive' dimension and not the 'motor' dimension that is of relevance for the modulation of response selection in conflicting situations.


## 1. Introduction

Fatigue is a major symptom in several neuroimmunological diseases (Kluger et al., 2013; Bansal et al., 2012; Greim et al., 2007) including neurosarcoidosis, a rare central nervous system

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manifestation of sarcoidosis (Lacomis, 2011) (incidence: 2:1,000,000). In neurosarcoidosis, macrophages release cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukins (IL), including IL-2, IL-6, IL-12, IL-15, IL-16 and IL-18 (Lacomis, 2011; Hoitsma et al., 2004). It is likely that fatigue in neurosarcoidosis emerges as a consequence of these immunological alterations, which have often been reported to underlie fatigue (for review: Bansal et al., 2012). Fatigue has been shown to be associated with dysfunctions in cognitive control processes (for review: Boksem and Tops, 2008; Capuron et al., 2005). Lorist and Jolij (2012) showed that the effects of fatigue on the ability to control conflicting information during response selection emerged as a consequence of deficits in top-down attentional processing (Boksem et al., 2006). Similar results have been reported by Van Den Eede et al. (2011) who showed that psychomotor functions are strongly compromised by fatigue. Psychomotor and cognitive control processes are known to be modulated by monoamines and especially the dopamine system (e.g. Willemssen et al., 2009). As the dopamine system has also been implicated in the emergence of fatigue (Lindqvist et al., 2013; Moeller et al., 2012; Meeusen and Roelands, 2010) it seems plausible that cognitive control processes are modulated by fatigue. Despite conclusive results showing an impact of fatigue on cognitive control functions it is unknown in how far fatigue modulates these important cognitive functions in neurosarcoidosis. However, fatigue is not a uni-dimensional construct but is composed of different features, some being more physical and motor-related and some being more cognitive in nature (e.g. Penner et al., 2009). Especially in the context of psychomotor functions and cognitive control this is important to distinguish, since both of these features may be critical for response monitoring functions. Goal of this study is therefore to examine which aspects of fatigue (cognitive or motor aspects) are most important for the modulation of response selection processes and possible deficits in cognitive control in neurosarcoidosis.

In the present study we investigate conflict monitoring and response selection processes in neurosarcoidosis patients and healthy controls in relation to cognitive and motor fatigue using neurophysiological techniques. Using event-related potentials (ERPs) conflict monitoring and response selection processes are reflected by the fronto-central N2 component (e.g. Folstein and Van Petten, 2008; Van Veen and Carter, 2002). We hypothesize that neurosarcoidosis patients are less capable to select between two antagonistic response tendencies. This deficit should be expressed by a reduced and/or delayed fronto-central N2 and by increased reaction times when confronted with two antagonistic response tendencies. Interindividual differences in response selection and conflict monitoring may be modulated on the basis of the interindividual degree of fatigue as previous results already report an effect of fatigue on conflict monitoring functions (Lorist and Jolij, 2012). We hypothesize that higher fatigue levels are related to stronger deficits during response selection in neurosarcoidosis patients and controls.

However, it is possible that also attentional selection processes are altered and modulate response selection processes. This is because TNF-α, for example, which has been shown to modulate mechanisms of visual attentional selection (Gajewski et al., 2013; Beste et al., 2010), is altered in neurosarcoidosis (Hoitsma et al., 2004) and plays a role in fatigue (e.g. Bansal et al., 2012). To examine the role of potentially altered attentional selection processes in neurosarcoidosis, we examine the visual P1 and N1 that are well-known to reflect visuo-perceptual (P1) and attentional selection processes (N1), respectively (e.g. Herrmann and Knight, 2001). Yet, we do not expect that these functions are altered in neurosarcoidosis and related to interindividual variations in the degree of fatigue. This is because fatigue has been shown to be closely related to the dopaminergic system (for review: Meeusen and Roelands, 2010), which only indirectly modulates bottom-up attentional selection processes and visuo-perceptual processes (Sarter et al., 2006), as measured using the N1 and P1.

Due to the neuroimmunological nature of this disease we further examine whether changes in above-mentioned cognitive subprocesses affected in neurosarcoidosis may be modulated by proinflammatory cytokines such as TNF-α and the soluble interleukin-2 receptor (sIL-2R). TNF-α and sIL-2R may be particularly relevant in this regard because these proinflammatory cytokines are assumed to play a major role in the pathogenesis of neurosarcoidosis (Lacomis, 2011; Petereit et al., 2010; Hoitsma et al., 2004) and have been found to be associated with fatigue in other neurological conditions (Lindqvist et al., 2013, 2012; Rudick and Barna, 1990).

## 2. Experimental procedures

### 2.1. Patients and participants

Thirty patients with neurosarcoidosis (NSA) were enrolled into the study. Five patients had to be excluded because of poor quality of the neurophysiological data in the experiment conducted to examine response selection processes. Data analysis was conducted with the remaining $N=25$ patients. Diagnosis of neurosarcoidosis was done according to the criteria proposed by Zajicek et al. (1999). Zajicek's category 'possible' is defined as neurological presentation and the exclusion of possible alternative diagnoses to NSA. The category 'probable' also includes proof of a systemic sarcoidosis (by biopsy including the Kveim test and/or two of the following indirect indicators: a Gallium scan, chest imaging and angiotensin-converting enzyme [ACE] in serum) and CNS inflammation (elevated proteins and/or cells, oligoclonal bands and/or a compatible MRI). The category 'definite' is established via a biopsy of the nervous system, neurological presentation and the exclusion of alternative diagnoses. We added laboratory parameters such as sIl-2R, TNF-α and b2-microglobulin in serum and cerebrospinal fluid (CSF) to obtain information about the actual inflammation status of the patient (Hoitsma et al., 2004). In the group of patients with neurosarcoidosis, 22 presented a probable diagnosis, and 3 presented a definite diagnosis. Detailed characteristics of the individual neurosarcoidosis patients are shown in Table 1. The neurosarcoidosis patients were recruited from the clinic and outpatient clinic of the Department of Neurology, St. Josef Hospital, Ruhr-Universität Bochum.

Together with this sample of neurosarcoidosis patients, a sample of case-matched healthy controls ($N=25$) was recruited by newspaper announcements. The cases were matched for age, sex and educational background.

To examine the impact of fatigue on conflict processing and response monitoring functions we used the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009). The FSMC is suitable to distinguish between 'cognitive' and 'motor' fatigue. The FSMC has a high sensitivity, specificity, reliability and validity. In addition to response selection processes we examined basic neuropsychological performance in neurosarcoidosis patients and controls using