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Modulatory effects of proinflammatory cytokines for action cascading processes – Evidence from neurosarcoidosis

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ABSTRACT

Neurosarcoidosis is a rare central nervous system manifestation of sarcoidosis. T cell, T-helper cell and macrophage activation via the major histocompatibility complex (MHC) II-mediated pathway causes this disease. Little is known about the possible cognitive disturbances in this disease as most reported instances are case studies. Here, we provide the first in-depth analysis of psychomotor functions in a sample of 30 neurosarcoidosis patients. We investigated action control processes using a paradigm that is able to examine how different tasks are cascaded to achieve the task goal. We integrated electrophysiological (EEG) data with behavioural and neuroimmunological data.

Our results show that there was no general cognitive decline in patients with neurosarcoidosis. Patients only presented deficits when two response options have to be prioritized. Patients apply an inefficient processing strategy where they try to processes different response options in parallel. The electrophysiological data show that the deficits are due to dysfunctions at the response selection stage. Behavioural and neurophysiological changes are predictable on the basis of soluble interleukin 2 receptor serum concentrations. The results show that neurosarcoidosis is not associated with nonspecific changes in cognitive functions but does lead to specific alterations in cognitive control that are strongly dependent on immunological parameters.

1. Introduction

Neurosarcoidosis is a rare neurological disorder and a central nervous system manifestation of sarcoidosis, a systemic granulomatous disease of undetermined origin (Lacomis, 2011). The incidence of sarcoidosis is 11 per 100,000 in Caucasians; however, the nervous system is affected and neurosarcoidosis is evident in approximately 5–13% of cases. The histopathologic lesions in neurosarcoidosis are noncaseating granuloma, which are thought to begin with T cell, T-helper cell and macrophage activation via a major histocompatibility complex (MHC) II-mediated pathway and can appear everywhere in the brain. In neurosarcoidosis, macrophages release cytokines, such as tumour 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). TNF-α is targeted in the course of treatment using biologicals (e.g., Lacomis, 2011; Santos et al., 2010; Morovan and Segal, 2009), and the disease can be reliably staged using interleukin-2 receptor (IL-2R) and soluble interleukin-2 receptor (sIL-2R) concentrations (Petereit et al., 2010; Hoitsma et al., 2004; Grutters et al., 2003).

Due to the rarity of neurosarcoidosis, most recorded instances are case studies. Therefore, virtually nothing is known about the possible cognitive disturbances in this disease. However, different lines of neuropsychiatric research suggest that alterations in the immunological parameters that play roles in neurosarcoidosis strongly affect psychomotor processes. In particular, sIL-2 receptor expression levels are elevated in psychiatric diseases with profound psychomotor symptoms such as schizophrenia (e.g., Potvin et al., 2008; Licinio et al., 1993). Moreover, TNF-α may also affect response selection and control processes (Beste et al., 2010, 2011; McAfoose and Baune, 2009). These effects on psychomotor and action control functions may emerge because sIL-2 receptors and TNF-α accumulate in the basal ganglia and prefrontal structures (Zalcman et al., 2012; McCoy and Tansey, 2008; Sriram et al., 2006), which are important for psychomotor functions, including action-monitoring processes (for review: Redgrave et al., 2010).

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Action monitoring is particularly important when different response options must be ordered to accomplish a goal (Mückschel et al., 2013; Beste et al., 2012). Recent results suggest that fronto-striatal loops play an important role in these processes. Striatal activity predicts the degree to which simultaneously upcoming response options can be prioritised and ordered (Ness and Beste, 2013). The importance of the striatum is further corroborated by clinical data. Under conditions of striatal dysfunctions, different response options are not ordered but are processed in parallel. This arrangement slows the execution of actions (Beste and Saft, 2013). Because immunological aberrations in neurosarcoidosis may compromise the integrity of the prefrontal-basal ganglia networks, we hypothesise that neurosarcoidosis is associated with dysfunctions in the processing of simultaneously upcoming response options. Using electrophysiological methods (event-related potentials, ERPs), Mückschel et al. (2013) showed that the degree of task ordering is reflected by the frontal P3, which is larger when different response options are not ordered (Mückschel et al., 2013). Hence, we hypothesise that the P3 will be larger in neurosarcoidosis patients. If these changes related to action control are an effect of altered cytokine serum concentrations, deficits in action control processes should be predictable on the basis of individual cytokine concentrations.

2. Materials and methods

2.1. Patients

According to the criteria proposed by Zajicek et al. (1999) for the diagnosis of neurosarcoidosis, we classified a group of 30 patients with neurosarcoidosis into categories of 'possible', 'probable' or 'definite' neurosarcoidosis. There were no drop-outs; i.e., all 30 patients screened took part in the study and gave written informed consent. We added laboratory parameters such as sIl-2R, TNF-α and b2-microglobulin in serum to obtain information about the actual inflammation status of the patient (Hoitsma et al., 2004).

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.

In the group of 30 patients with neurosarcoidosis, 4 presented a possible diagnosis, 23 presented a probable diagnosis, and 3 presented a definite diagnosis. Patients in the 'possible' category were included because of bioptically proven systemic sarcoidosis and neurological presentation. Detailed characteristics of the individual neurosarcoidosis patients are shown in Table 1.

Together with this sample of neurosarcoidosis patients, a sample of case-matched healthy controls ($N = 30$) was recruited. The cases were matched for age, sex and educational background. The NSA group had no other co-morbid conditions that were medicated. The control group also showed no intake of medication. There were no differences in antidepressant status. Body weight data was not collected. The BMI was hence not controlled, which is a limitation of the study. In addition to the cognitive-neurophysiological testing of task ordering processes, the neurosarcoidosis patients and controls underwent standard neuropsychological examination using the "digit-span" (forward and backward) to estimate short-term memory, the "trial-making test (A/B)" to assess processing speed and interference control, and the Beck Depression Inventory (BDI) to assess depressive symptoms and the Mehrfachwahl Wortschatz test (MWT-B) to assess the level of pre-morbid intelligence. We only used the overall score, since we have no specific hypotheses why some subscales are more important than others and because 'depression' is not of primary interest to this study. Moreover, the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) was used to examine the degree of fatigue usually observed in (neuro)sarcoidosis. The study was approved by the ethics committee of the Ruhr-University of Bochum. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Experimental paradigm, EEG recording and analysis

To study action selection in BHC we used a Stop-change paradigm. With this paradigm it is possible to examine the processing mode of action cascading by analyzing reaction time data using mathematical constraints (cf. Mückschel et al., 2013; Verbruggen et al., 2008). The full details can be found in the Supplemental material. One aspect in the task is "stopping" of one reaction and the other aspect is switching to another task (i.e., task-switching processes). In this respect the applied task is a hybrid of a stop-paradigm and a task switching paradigm (see also: Verbruggen et al., 2008). The paradigm is shown in Fig. 1.

The participants are required to respond to a visual stimulus. In 30% of cases movement execution is interrupted by another visual stimulus and participants are required to stop the ongoing response. In these cases an auditory stimulus is additionally presented signalling to execute an alternative response. This auditory 'change stimulus' is either presented at the same time of the stop stimulus, or with a stimulus onset asynchrony of 300 ms. These different conditions are used to calculate a reaction time value (slope of the reaction times) that indicates the mode of response selection of a serial-parallel continuum. In case of a more serial processing mode the slope is flatter (closer to 0), in case of a more parallel processing mode the slope is steeper (closer to −1).

EEG was recorded from 65 Ag–AgCl electrodes at standard scalp positions against a reference electrode located at FCz. After data preprocessing (filtering, artifact rejection, re-referencing, baseline correction) the data was segmented stimulus-locked on the presentation of the stop signal. Based upon this stimulus-locking procedure, the P1, N1 and P3 ERPs were quantified at the single subject level. Further details of the experimental setup and EEG data analysis procedures can be found in the Supplemental material.

2.3. Measurement of laboratory parameters

Soluble IL-2R (an established marker for inflammatory activity in patients with SA/NSA (reference value <710 U/ml)) and soluble TNF-α (a frequent/common proinflammatory cytokine (reference value <8.1 ng/l)) were measured in serum samples according to an automatic procedure of a solid-phase two-site chemiluminescent immunometric assay via the Siemens IMMULITE 1000 Analyzer (Siemens, Inc. Erlangen, Germany). ACE, an established SA/NAS marker in serum, was measured photometrically in the serum via an ACE colour analyser (Fujirebio Inc.) adapted on a Konelab Analyzer with a reference value between 8 and 28. The coefficient of variation for soluble IL-2R was 3.56 and 3.68 for test and re-test, respectively. The coefficient of variation for soluble TNF-α was 6.45 and 6.69 for test and re-test, respectively. For ACE the coefficient of variation was 2.44 and 2.55 for test and re-test, respectively. The re-test reliability for ACE, soluble IL-2R and soluble TNF-α was $r > .91$.

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