NeuroImage: Clinical 10 (2016) 89–95

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cortical thinning in the anterior cingulate cortex predicts multiple sclerosis patients' fluency performance in a lateralised manner

Olivia Geisseler[a,b,*], Tobias Pflugshaupt[a,c,1], Ladina Bezzola[d], Katja Reuter[a], David Weller[a], Bernhard Schuknecht[e], Peter Brugger[a], Michael Linnebank[a,f,1]

[a]Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland
[b]Department of Psychology, University of Zurich, Binzmühlestrasse 14/1, 8050 Zürich, Switzerland
[c]Neurology and Neurorehabilitation Center, Luzerner Kantonsspital, 6016 Luzern, Switzerland
[d]URPP Dynamics of Healthy Aging, University of Zurich, Andreasstrasse 15/Box 2, 8050 Zurich, Switzerland
[e]Medizinisch Radiologisches Institut, Bahnhofplatz 3, 8001 Zurich, Switzerland
[f]Department of Neurology, Helios-Klinik Hagen-Ambrock, Ambrocker Weg 60, 58091 Hagen, Germany

ARTICLE INFO

Article history:
Received 23 July 2015
Received in revised form 10 November 2015
Accepted 12 November 2015
Available online 14 November 2015

Keywords:
Multiple sclerosis
Executive function
Fluency
Atrophy
Cortical thinning

ABSTRACT

Cognitive impairment is as an important feature of Multiple Sclerosis (MS), and might be even more relevant to patients than mobility restrictions. Compared to the multitude of studies investigating memory deficits or basic cognitive slowing, executive dysfunction is a rarely studied cognitive domain in MS, and its neural correlates remain largely unexplored. Even rarer are topological studies on specific cognitive functions in MS. Here we used several structural MRI parameters – including cortical thinning and T2 lesion load – to investigate neural correlates of executive dysfunction, both on a global and a regional level by means of voxel- and vertex-wise analyses. Forty-eight patients with relapsing-remitting MS and 48 healthy controls participated in the study. Five executive functions were assessed, i.e. verbal and figural fluency, working memory, interference control and set shifting. Patients scored lower than controls in verbal and figural fluency only, and displayed widespread cortical thinning. On a global level, cortical thickness independently predicted verbal fluency performance, when controlling for lesion volume and central brain atrophy estimates. On a regional level, cortical thinning in the anterior cingulate region correlated with deficits in verbal and figural fluency and did so in a lateralised manner: Left-sided thinning was related to reduced verbal – but not figural – fluency, whereas the opposite pattern was observed for right-sided thinning. We conclude that executive dysfunction in MS patients can specifically affect verbal and figural fluency. The observed lateralised clinico-anatomical correlation has previously been described in brain-damaged patients with large focal lesions only, for example after stroke. Based on focal grey matter atrophy, we here show for the first time comparable lateralised findings in a white matter disease with widespread pathology.

1. Introduction

Multiple Sclerosis (MS) is a chronic demyelinating disease affecting all parts of the central nervous system. It used to be characterised primarily by its sensory, motor and visual symptoms. However, cognitive impairment is now recognised as an important feature of MS, prevalent in 43–70% of patients (Chiaravalloti and DeLuca, 2008). It might even be more relevant to patients than mobility restrictions (Amato et al., 2006). As MS has usually an early onset in young adult life (Calabrese, 2006), cognitive impairment significantly contributes to patients' disability status, is critical for working capacity, and thus negatively affects quality of life (Rao et al., 1991). Processing speed and episodic memory seem the most prominent cognitive features of MS (Chiaravalloti and DeLuca, 2008); however, MS patients often exhibit significant deficits in executive functions too (Drew et al., 2008). Although the latter can have devastating effects on patients' everyday life, their level of independence and societal costs (Amato et al., 2013), studies examining executive deficits in MS patients are relatively rare (Foong et al., 1997; Henry and Beatty, 2006; Radomski et al., 2015),

Abbreviations: EDSS, Expanded Disability Status Scale; FDR, false discovery rate; FLAIR, fluid attenuated inversion recovery; MPRAGE, magnetization prepared rapid gradient-echo imaging; MS, multiple sclerosis; TVW, third ventricle width; VLSM, voxel-lesion symptom mapping.

* Corresponding author at: Department of Neurology, Neuropsychology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland.
E-mail addresses: Olivia.geisseler@usz.ch (O. Geisseler), Tobias.pflugshaupt@luks.ch (T. Pflugshaupt), l.bezzola@psychologie.uzh.ch (L. Bezzola), katja.reuter@usz.ch (K. Reuter), david.weller@usz.ch (D. Weller), image-solution@ggaweb.ch (B. Schuknecht), peter.brugger@usz.ch (P. Brugger), michael.linnebank@helios-kliniken.de (M. Linnebank).
[1] Present address.

http://dx.doi.org/10.1016/j.nicl.2015.11.008

compared to the multitude of studies investigating memory deficits or basic cognitive slowing (e.g. Chiaravalloti and DeLuca, 2008; Rogers and Panegyres, 2007; Roth et al., 2015). Traditionally, MS has been thought of as a white matter disease, with focal demyelinating lesions in the white matter being the pathological hallmark. However, this view has been challenged in recent years. It is now known that grey matter areas including the cerebral cortex can also be affected (Calabrese et al., 2012), a finding demonstrated first in post-mortem analyses (Kidd et al., 1999). In addition to focal lesions, brains of MS patients sometimes show considerable atrophy (Barkhof, 2002), which affects not only white, but also grey matter structures. Atrophy can become manifest, for example, as widespread cortical thickness reduction, with a predominant involvement of temporal and frontal regions (Calabrese et al., 2010; Narayana et al., 2013; Sailer et al., 2003).

Modern MRI techniques and post-processing methods assessing atrophy parameters contribute to the improvement in understanding the mechanisms responsible for physical and cognitive impairment in MS (Filippi and Rocca, 2010). During the last three decades, many studies have demonstrated an association between white matter pathology and cognitive impairment (e.g. Rao et al., 1989). However, only modest correlations were found (e.g. Foong et al., 1997; Swirsky-Sacchetti et al., 1992), so that a majority of variance in cognitive performance remained unexplained. MRI markers of atrophy such as increased third ventricle width or reduced total white and grey matter volumes are consistently found to correlate more strongly with cognitive deficits (Amato et al., 2004; Benedict et al., 2006) than white matter lesion load. In the last decade, grey matter pathology, i.e. cortical and deep grey matter atrophy and cortical lesion load, has been identified as a significant substrate of cognitive impairment, by showing particularly strong associations (e.g. Amato et al., 2004; Calabrese et al., 2009; Nielsen et al., 2013; Zivadinov et al., 2001).

Despite the huge amount of correlation studies between different structural alterations and cognitive dysfunction in MS, focal–topological studies on specific cognitive functions are rare. For example, deficits in sustained attention and working memory were related to lesions in bilateral frontal and parietal white matter (Sperling et al., 2001), and deficits in verbal learning to lesions in the left frontal lobe (Reuter et al., 2011). With regard to atrophy, bilateral hippocampal atrophy has been related to impaired verbal learning (Sicotte et al., 2008).

The aim of the present study was to investigate executive dysfunction in patients with MS and to analyse its relationship with both global and regional MRI markers. Our methodological focus was on cortical thinning. Only few previous studies have addressed the identification of cortical thinning in MS and its association to global cognitive impairment (Calabrese et al., 2010; Morgen et al., 2006; Tekok-Kilic et al., 2007). And to the best of our knowledge, only a single study so far investigated the impact of regional cortical thinning on specific cognitive disability, showing that focal thinning in the bilateral fusiform gyrus was related to impaired processing of facial expressions (Mike et al., 2013). Here we extend this approach by examining whether similar foci can be found for MS-related executive dysfunction.

2. Materials and methods

2.1. Participants

Forty-eight patients with a definite diagnosis of MS according to the McDonald 2010 criteria (Polman et al., 2011) and a relapsing–remitting course were recruited at the Multiple Sclerosis Centre of the University Hospital of Zurich. Forty-seven patients (98%) were treated with an immunomodulatory drug — 32 with natalizumab, ten with beta-interferons, three with fingolimod, one with glatiramer acetat, one with dimethylfumarate, and one patient had no disease-modifying therapy. We applied the following exclusion criteria: a) relapse or steroid-treatment during the last two months, b) current or past neurological disorder in addition to multiple sclerosis, c) psychiatric disorder apart from multiple sclerosis-related depressive mood state, d) a reading-relevant visual acuity deficit, e) a writing- and/or drawing-relevant upper limb sensorimotor impairment of the dominant hand and f) dysarthria. Furthermore, 48 age-, gender-, handedness-, and education-matched healthy controls without previous or present history of neurological or psychiatric dysfunction were included. The study was approved by the regional Ethics Committee. All participants provided written informed consent. Control participants received financial compensation for their attendance.

2.2. Neuropsychological and neurological examination

Neuropsychological and neurological (only for the patient group) examinations were performed within one month of the MRI scan described below by experienced clinicians of the Multiple Sclerosis Centre. Five executive functions were examined. First, verbal-phonematic fluency was assessed with the Regensburger verbal fluency test (Aschenbrenner et al., 2000). Participants were required to generate as many words as possible beginning with the letter “s” in two minutes. Repetitions of word stems or deviations from test rules were regarded as errors; the number of correct answers was further analysed. The HAMASCH-five-points-test (Haid et al., 2002) was applied to assess figural fluency (Regard et al., 1982). This test required participants to create as many unique designs as possible through connecting at least two dots of a five-dot pattern with straight lines within three minutes. The total number of unique designs entered further analyses. Furthermore, working memory was assessed by a two-back task (Zimmermann and Fimm, 2007), where the total number of errors (number of misses plus number of false positives) was further analysed. The Colour-Word-Interference subtest of the Delis–Kaplan Executive Function System (Delis et al., 2001) was used to investigate response inhibition and set shifting. In the interference condition, participants had to name the colour of the ink in which the word was printed – which is at conflict with the word meaning – while inhibiting the propensity to read the word. In the switching condition, participants had to irregularly alternate between reading the word and naming the ink, depending on the presence or absence of a box surrounding the word. Again, ink colour and word meaning were always at conflict with one another. Furthermore, a third condition of the D-KEFS colour-word interference test, i.e. the colour naming condition, served as a control parameter for basic information processing speed. As this study focuses on executive functions rather than on basic cognitive slowing, corrected time-to-completion indices were calculated with this latter parameter, according to the procedure specified by Delis and colleagues (2001). In other words, and concerning both interference control and set shifting, two variables entered further analyses, i.e. the number of correct answers and the corrected time-to-complete. Moreover, participants had to complete a German version (Hautzinger and Bailer, 1992) of the CES-D Depression questionnaire (Radloff, 1977) and the Würzburg Fatigue Inventory (WEIMuS) (Flachenecker et al., 2008) to self-assess depressive symptoms as well as cognitive and physical fatigue during the last week. Similar to other studies (Sumowski et al., 2014), cognitive reserve was examined with vocabulary knowledge. In our study, the Multiple-Choice Word Test-B (Lehrl, 2005) was applied. Additionally, Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983) were obtained in all patients.

2.3. MR image acquisition protocol

All images were acquired with a neuro-optimised 1.5 Tesla MR scanner (Siemens Magnetom AvantoTM) equipped with a SQ-engine gradient (45 m/T/m @ 200 T/m/s) using a dedicated 32-channel head coil. The sequences acquired in each subject included a T1-weighted Magnetisation Prepared Rapid Gradient Echo (MPRAGE; voxel size = 1 x 1 x 1 mm, slice thickness = 1 mm, repetition time = 2420 ms, echo time = 4.18 ms,