NeuroImage: Clinical 20 (2018) 844–850

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Is impaired information processing speed a matter of structural or functional damage in MS?

K.A. Meijer*, Q. van Geest, A.J.C. Eijlers, J.J.G. Geurts, M.M. Schoonheim, H.E. Hulst

Department of Anatomy and Neurosciences, MS Centres Amsterdam, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Multiple sclerosis
Cognition/IPS
fMRI
DTI
Volumetric MRI

ABSTRACT

Objective: Cognitive deficits, especially those of information processing speed (IPS), are common in multiple sclerosis (MS), however, the underlying neurobiological mechanisms remain poorly understood. In this study, we examined structural and functional brain changes separately, but also in an integrative manner, in relation to IPS performance.

Methods: IPS was measured using the symbol digit modalities test (SDMT) in 330 MS patients and 96 controls. Patients with IPS impairment (IPS-I, z-score < -1.5) were compared to patients with preserved IPS performance (IPS-P) on volumetric measures, white matter integrity loss (using diffusion tensor imaging) and the severity of functional connectivity changes (using resting-state fMRI). Significant predictors of IPS performance were used to create groups of mild or severe structural and/or functional damage to determine the relative effect of structural and/or functional changes on IPS.

Results: IPS-I patients, compared to IPS-P patients, showed lower deep gray matter volume and less WM integrity, but stronger increases in functional connectivity. Patients with predominantly structural damage had worse IPS (z-score $= -1.49$) than patients with predominantly functional changes (z-score $= -0.84$), although both structural and functional measures remained significant in a regression model. Patients with severe structural *and* functional changes had worst IPS (z-score $= -1.95$).

Conclusion: The level of structural damage explains IPS performance better than functional changes. After integrating functional and structural changes, however, we were able to detect more subtle and stepwise decline in IPS. In subgroups with a similar degree of structural damage, more severe functional changes resulted in worse IPS scores than those with only mild functional changes.

1. Introduction

Multiple sclerosis (MS) is a progressive inflammatory and neurodegenerative disease of the central nervous system characterized by demyelination and neuronal loss (Stys et al., 2012). In addition to physical disabilities, cognitive deficits are common, affecting approximately 40–70% of the MS patients (Amato et al., 2006; Chiaravalloti and DeLuca, 2008). Among cognitive deficits, problems with information processing speed (IPS) are frequently seen and already present early in the disease (Archibald and Fisk, 2000; Deloire, 2005; Chiaravalloti and DeLuca, 2008; Khalil et al., 2011).

In MS, previous imaging studies have shown that IPS deficits are related to structural or functional brain abnormalities (Benedict et al., 2005; Dineen et al., 2009; Khalil et al., 2011; Leavitt et al., 2012; Schoonheim et al., 2013, 2014; Bergsland et al., 2016; Moroso et al., 2017), including deep gray matter (DGM) atrophy (Batista et al., 2012) and white matter (WM) integrity loss (Dineen et al., 2009), as well as changes in functional connectivity (Leavitt et al., 2012; Schoonheim et al., 2013). Unfortunately, studies that have integrated structural and functional measures to explain IPS deficits are currently lacking. Although structural and functional brain characteristics are intertwined to a certain extent, there is no simple one-to-one relation between these two (Hillary and Grafman, 2017). Therefore, it might be that structural damage may occur in the presence of minor functional changes, but may also involve severe functional changes. As complex cognitive functions like IPS arise from an efficient interplay between the brains' functional and structural architecture, varying levels of structural and/or functional damage may also result in different levels of IPS impairment in MS (Park and Friston, 2013). This emphasizes the need to consider both structural and functional measures simultaneously to be able to better understand IPS deficits.

We hypothesize that to increase our understanding of the

* Corresponding author at: VU University Medical Center, Department of Anatomy and Neurosciences, PO Box 7057, 1007 MB Amsterdam, the Netherlands.
E-mail address: k.meijer@vumc.nl (K.A. Meijer).

https://doi.org/10.1016/j.nicl.2018.09.021
Received 7 May 2018; Received in revised form 20 August 2018; Accepted 24 September 2018
Available online 26 September 2018

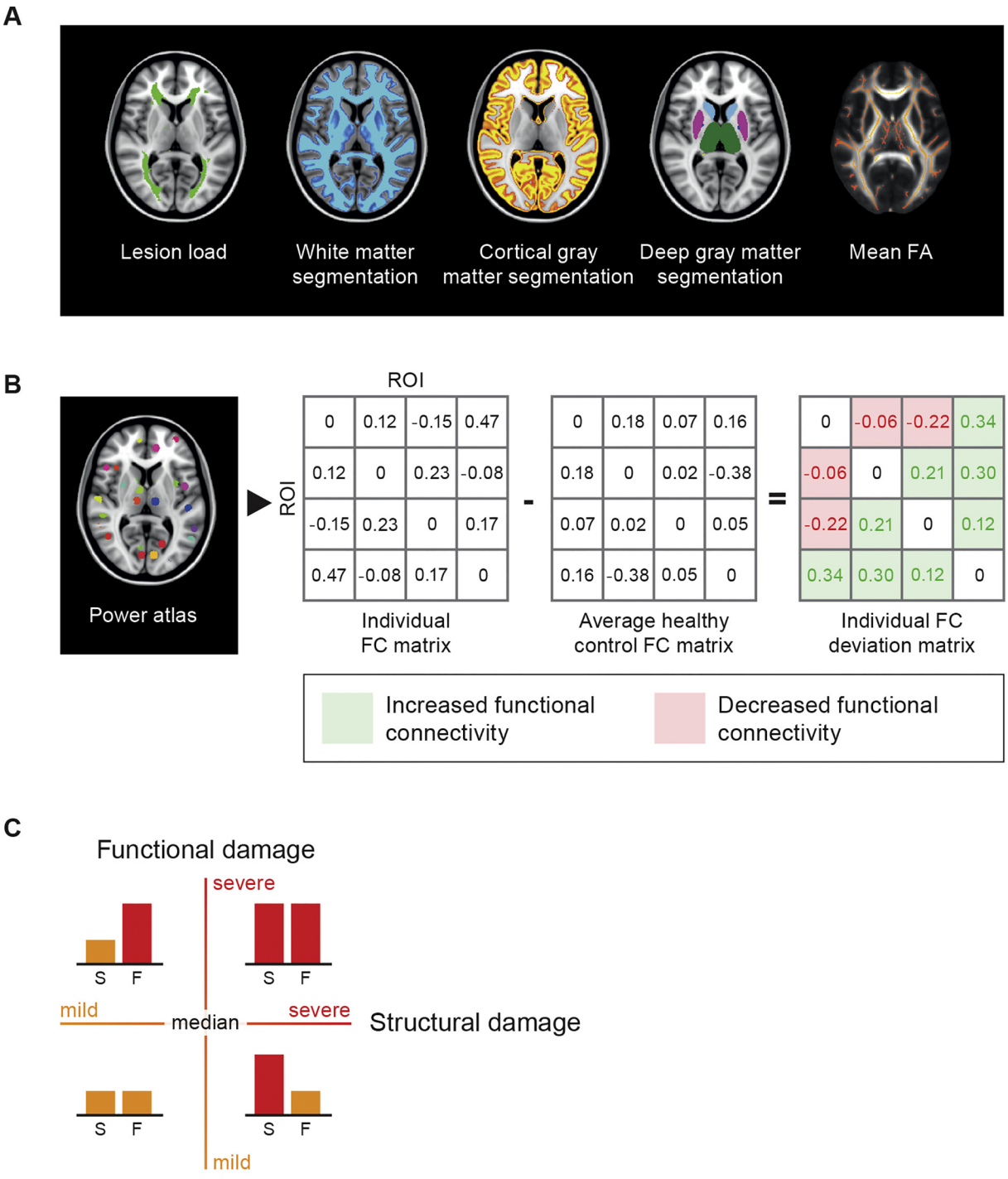

Fig. 1. Data analysis flow chart. To define the structural brain status, the most commonly addressed global structural measures were determined, including brain volumes, lesion load and whole-brain white matter integrity (A) We subsequently aimed to design a whole-brain functional network measure representing the severity of functional connectivity changes in each individual. To compute a measure that could reflect the whole-brain functional brain status, an average healthy control matrix was computed. This matrix was subsequently subtracted from the individual functional connectivity matrices resulting in an individual deviation matrix. An example matrix consisting of the connectivity values between four regions is shown (B). Patients were assigned to one of the four groups based on their level of structural and functional changes (C).

underlying neurobiology of IPS deficits an integrated measure of functional and structural brain changes is essential, instead of studying either one or the other (Chard and Trip, 2017). Therefore, we integrated advanced functional and structural MRI measures to examine the relative and joint impact of functional and structural brain changes in explaining IPS performance.

2. Methods

2.1. Participants

All participants with complete functional and structural imaging protocols (see below) of the Amsterdam MS Cohort (Daams et al., 2015; Schoonheim et al., 2015) were included, resulting in 330 MS patients (age 48.14 ± 10.06 years) and 96 healthy controls (HC; age