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Random number generation deficits in patients with multiple sclerosis: Characteristics and neural correlates

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ABSTRACT

Human subjects typically deviate systematically from randomness when attempting to produce a sequence of random numbers. Despite an increasing number of behavioral and functional neuroimaging studies on random number generation (RNG), its structural correlates have never been investigated. We set out to fill this gap in 44 patients with multiple sclerosis (MS), a disease whose impact on RNG has never been studied. The RNG task required the paced (1 Hz) generation of the numbers from 1 to 6 in a sequence as random as possible. The same task was administered in 39 matched healthy controls. To assess neuroanatomical correlates such as cortical thickness, lesion load and third ventricle width, all subjects underwent high-resolution structural MRI. Compared to controls, MS patients exhibited an enhanced tendency to arrange consecutive numbers in an ascending order ("forward counting"). Furthermore, patients showed a higher susceptibility to rule breaks (producing out-of-category digits like 7) and to skip beats of the metronome. Clinico-anatomical correlation analyses revealed two main findings: First, increased counting in MS patients was associated with higher cortical lesion load. Second, increased number of skipped beats was related to widespread cortical thinning. In conclusion, our test results illustrate a loss of behavioral complexity in the course of MS, while the imaging results suggest an association between this loss and cortical pathology.

Abbreviations: FOD, first-order differences; MDT, mental dice task; MS, multiple sclerosis; RNG, random number generation; ROI, region of interest; RRMS, relapsing-remitting multiple sclerosis; TPI, turning point index; WM, white matter.

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1. Introduction

As smart human brains are in spotting patterns and following rules, as miserably they fail in attempting to be unpredictable. A case in point is our inability to generate random sequences of responses. Instructions of a random number generation (RNG) task require subjects to arrange numbers in a sequence "as random as possible", implicitly asking to avoid any algorithm and to disobey any rule. Under a huge range of conditions (Brugger, 1997) healthy volunteers were found unable to follow these instructions, and so were patients with various neuropsychiatric diseases (Brown, Soliveri, & Jahanshahi, 1998; Brugger, Monsch, Salmon, & Butters, 1996; Ho, Sahakian, Robbins, & Barker, 2004; Salamé & Danion, 2007; Spatt & Goldenberg, 1993). A limited capacity of working memory and executive functions have been implied in the failure to produce unpredictable, or random sequences of response alternatives (Baddeley, 1966, 1998; Joppich et al., 2004; Maes, Eling, Reelick, & Kessels, 2011; Miyake et al., 2000). Neuroimaging studies have largely supported the assumed implication of the (pre)frontal lobes for RNG (Artiges et al., 2000; Itagaki, Niwa, Itoh, & Momose, 1995) and non-invasive intervention methods have suggested their causal involvement (Jahanshahi et al., 1998; Knoch, Brugger, & Regard, 2005).

Facing the large and rapidly growing number of behavioral and functional neuroimaging studies on RNG, one is left wondering why the neuroanatomical correlates of RNG have never been examined in a structural imaging approach. The present study was aimed at filling this gap in patients with multiple sclerosis (MS), a disease whose impact on RNG has, to the best of our knowledge, never been studied. MS, the most common autoimmune disorder affecting the central nervous system, is historically considered a white matter (WM) disease, with focal demyelinating lesions in the WM being the pathological hallmark. However, several recent neuropathological studies disclosed a relevant involvement of gray matter areas including the cerebral cortex (Calabrese et al., 2015; Geisseler et al., 2016). Brain integrity, captured by various imaging techniques, has been shown to correlate with cognitive impairment (for review see Rocca et al., 2015), which is recognized as an important feature of MS, prevalent in 43–70% of MS patients (Chiaravalloti & DeLuca, 2008; Pflugshaupt, Geisseler, Nyffeler, & Linnebank, 2016). Although processing speed (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Roth, Denney, & Lynch, 2015) and episodic memory (e.g., Rogers & Panegyres, 2007) seem to be the most prominent cognitive feature of MS, these patients often exhibit significant deficits in executive functions (Geisseler et al., 2016; Henry & Beatty, 2006). Against this background, it appears tempting to assume that MS patients exhibit impaired performance in generating random sequences of numbers.

The aim of the present study is two-fold. On the one hand, we planned to examine the impact of MS on randomization performance; on the other hand, we wanted to explore, for the first time, structural brain correlates of RNG. Specifically, we predicted an impaired randomization performance by the patients with MS relative to a carefully matched healthy control group. As a first step in uncovering the neuroanatomical correlates of RNG, we planned to analyze associations between brain structure and RNG performance in healthy participants and, in the patient group, between cortical and subcortical damage and RNG performance.

2. Material and methods

2.1. Participants

Forty-four patients with a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the 2010 McDonald criteria (Polman et al., 2011) and 39 age-, gender-, handedness- and education-matched healthy controls participated in this study. Inclusion criteria for the patient group were no relapse or steroid-treatment during the last two months, no current or past neurological disorder in addition to MS, and no psychiatric disorders apart from MS-related depressive mood state. The local ethics committee approved the study, and all subjects gave written informed consent before participation. Control participants received financial compensation.

2.2. RNG task, performance measures and hypotheses

The mental dice task (MDT) was administered in its standardized form (Brugger et al., 1996). Subjects were instructed to imagine repeatedly throwing a die and to orally report the number that would show up, i.e., they had to generate numbers from 1 to 6 in a random fashion. Subjects were instructed to synchronize their response with a pacing auditory stimulus, which was a beeping sound presented at 1 Hz. A total of 66 valid responses were recorded.

While there are many different measures of (non) randomness, we focused on three variables, which were calculated by means of a freely available computer program (http://www.lancs.uk/staff/towse/rgcpage.html). First, we determined the distribution of first-order differences (FODs), reflecting the arithmetic difference between each response and the preceding one. Thus, FODs may vary between −5 (6 followed by 1) and +5 (1 followed by 6). The elegance of FODs is that their graphical depiction clearly illustrates the frequencies of all named combinations of the digits to be randomized in one curve (see Fig. 1). For the present purpose, it thus displays those pairs of consecutive numbers for which group differences were predicted alongside those for which no such differences were predicted. Specifically, FOD values of +1 reflect a counting strategy, which we predicted to be pronounced in patients with MS, under the assumption of an impaired executive control of automatized responding (i.e., counting). Some authors have reported an excess of counting in steps of 2 (FOD = +2), in addition to counting in the narrow sense (i.e., in steps of 1; Jahanshahi et al., 1998) and the display would allow us to check for the frequency of +2 pairings as well. FOD values of 0 represent the number of direct repetitions of any of the 6 digits to be randomized. We predicted a comparable degrees of repetition avoidance for both groups, as repetition (alternation) behavior may be under hippocampal, rather than prefrontal control (Lalonde, 2002). A second