Cognitive phenotypes predict response to restorative cognitive rehabilitation in multiple sclerosis

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Short Report

Cognitive phenotypes predict response to restorative cognitive rehabilitation in multiple sclerosis

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Abstract

Background: Cognitive phenotyping may be useful for predicting rehabilitation response in multiple sclerosis.

Objective: To evaluate the association between cognitive phenotype(s) and response to restorative cognitive rehabilitation (RRCR).

Methods: In a post hoc retrospective analysis of the RRCR study including 51 multiple sclerosis patients, we evaluated both impairment within specific cognitive domains as well as overall global impairment severity to investigate their relationship to improvement following rehabilitation.

Results: Greater improvement in executive function was predicted by impairment within this domain as well as by having fewer impaired cognitive domains overall. Similar results were observed for visuospatial memory.

Conclusions: Patients most likely to benefit from restorative cognitive rehabilitation may exhibit impairment within the domain of interest yet lower cognitive burden overall.

Keywords: Cognitive phenotypes, cognitive rehabilitation

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Introduction

Cognitive impairment affects patients with multiple sclerosis (MS) from the earliest stages of the disease, with a dramatic impact on quality of life.[1] However, it can be mitigated using cognitive rehabilitation. In order to maximize improvement in cognition after rehabilitation and avoid ineffective treatments, research in predicting response to rehabilitation is needed.[2] Our recent work identified clinical and magnetic resonance imaging (MRI) predictors of response to cognitive rehabilitation.[3,4] In light of the latest evidence provided on the conceptualization of specific cognitive phenotypes in MS[5,6] as a meaningful measure of cognitive status that can guide the direction of treatment and rehabilitation strategies,[7] we aimed to identify the cognitive phenotype(s), in terms of profile and severity of impairment, of patients more likely to benefit from home-based restorative cognitive rehabilitation.

Methods

Study participants

We conducted a retrospective post hoc analysis of a single-arm repeated-measures study on response to restorative cognitive rehabilitation (RRCR).[3,4] Fifty-one MS patients underwent a comprehensive neuropsychological assessment before and after treatment. Treatment was a home-based restorative cognitive rehabilitation program (BrainHQ, Posit Science Corporation), using a variety of adaptive daily cognitive exercises targeting a range of cognitive domains, including processing speed, visuospatial abilities, attention, and executive function.

Cognitive evaluation and outcomes

The neuropsychological assessment included the Brief International Cognitive Assessment for MS (BICAMS)[8] and, in addition, executive function tests

Table 1. Prevalence of patients subgrouped considering their baseline cognitive phenotypes and types of domain impairment for patients with single-domain and bi-domain impairment.

Baseline cognitive phenotype	*n* (%)	Baseline domain impairment, *n* (%)		
		MEM	ATT/IPS	EF
Preserved	26 (51)	0 (0%)		
Single-domain	9 (18)	1/9 (11%)	2/9 (22%)	6/9 (67%)
Bi-domain	10 (20)	7/10 (70%) [3 MEM + ATT/IPS] [4 MEM + EF]	6/10 (60%) [3 ATT/IPS + MEM] [3 ATT/IPS + EF]	7/10 (70%) [4 EF + MEM] [3 EF + ATT/IPS]
Multi-domain	6 (12)	6 (100%)		

MEM: memory; ATT/IPS: attention/information processing speed; EF: executive function.

from the Delis-Kaplan Executive Function System (DKEFS)[9] to have a better representation of cognitive functioning. Performance was grouped based on cognitive domains:[5] memory, attention/information processing speed, and executive function.

We addressed the question of cognitive phenotypes by accounting for both the severity and the typology of cognitive impairment. Phenotypes of cognitive status, in terms of impairment severity, were computed considering z-scores of each patient with a threshold of −1 standard deviation (SD).[5] This cutoff for impairment was chosen for the following reasons: consistency with previous works with this sample[3,4] and consistency with proposed phenotype taxonomies by Hancock et al.[5] Patients were considered preserved if z-scores were above −1 SD in all cognitive tests, otherwise mild cognitive impairment was determined if patients failed tests belonging to one domain (single-domain impairment), two domains (bi-domain impairment), or all three domains (multi-domain impairment).[5] Moreover, we also computed a variable representing the level of baseline impairment for each cognitive test that was considered in the subsequent statistical analyses.

Statistical analyses

The study sample was not sufficiently large to analyze post-rehabilitation improvement on a patient-by-patient basis in terms of cognitive phenotypes. Instead, to leverage our data set for this question, we performed statistical analyses on a group level which accounted for cognitive phenotypes by combining the severity of global cognitive impairment (i.e. the number of affected domains) with the degree of impairment within each unique cognitive domain. First, regression models were applied to evaluate the association between baseline cognitive performance in each test and pre-post change on the same test. Then analyses of covariance were conducted to compare pre-to-post rehabilitation change within each cognitive test in patients with different levels of global impairment while also considering impairment in the cognitive test. All analyses were completed controlling for treatment compliance.

Results

The sample ($n = 51$) comprised 26 cognitively preserved and 25 cognitively impaired patients: 9 single-domain impaired, 10 bi-domain impaired, 6 multi-domain impaired (Table 1). See previous publications for more details about the sample.[3,4]

Significant results for both severity and typology of impairment were found, identifying the cognitive phenotype of patients with greater improvement after cognitive rehabilitation.

More severe impairment in executive function at baseline predicted greater pre-post improvement within this domain after treatment (all DKEFS tests: card sorting test $p = 0.004$, tower test: $p = 0.002$, verbal fluency test: $p = 0.047$). In conjunction with this, patients with alterations in any single-domain showed the highest executive function improvement relative to bi-domain and multi-domain impaired patients (DKEFS card sorting test: correct sorts $p < 0.001$, description score $p = 0.04$), accounting for impairment specific to the evaluated domain. Preserved patients showed a higher improvement as well (correct sorts $p = 0.003$). Worse baseline visuospatial memory performance (Brief Visuospatial Memory Test-Revised, BVMT-R) also predicted greater improvement within this memory domain ($p < 0.001$) (Figure 1).

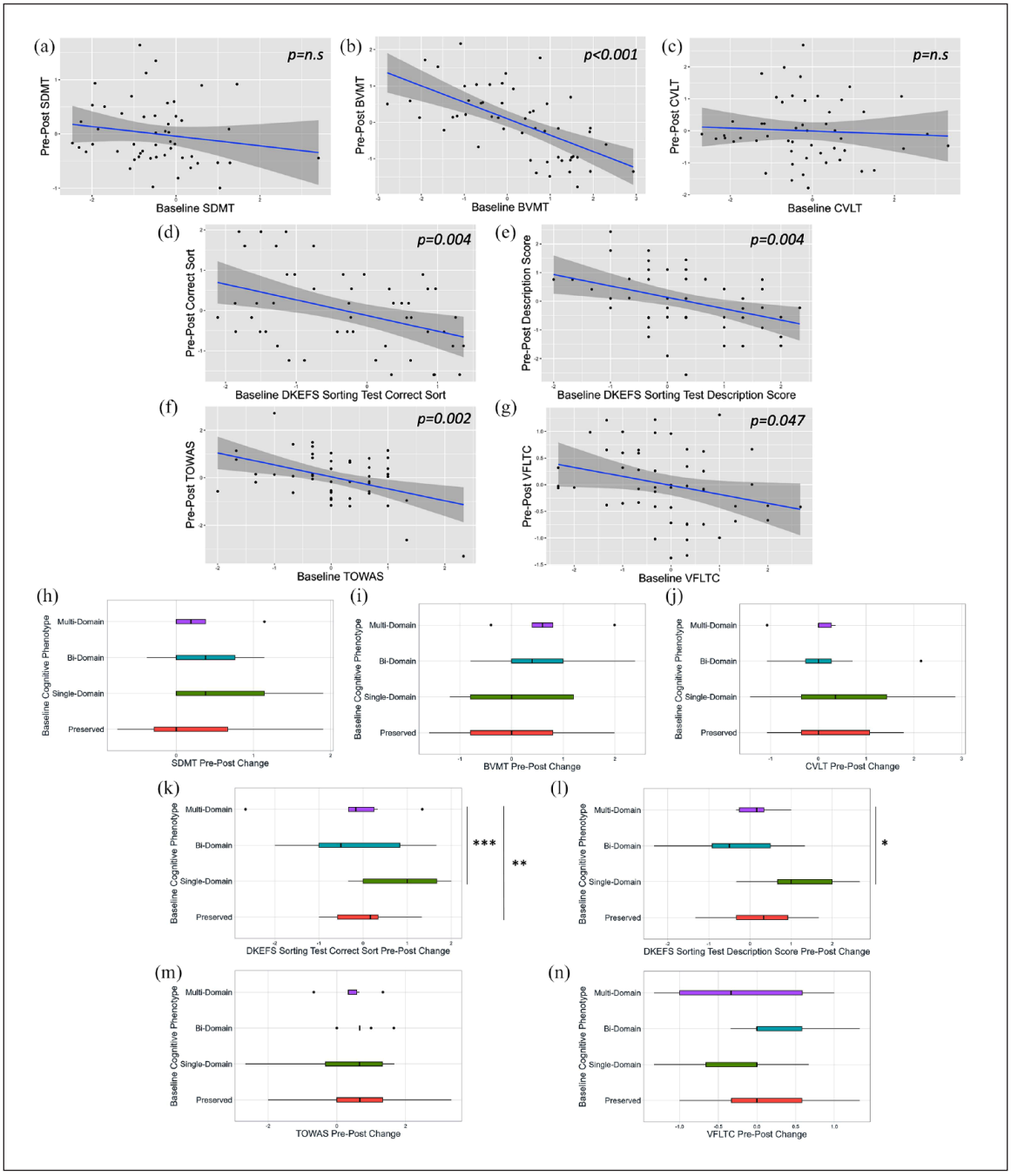

Figure 1. (a–g) Scatter plots representing associations between baseline cognitive performance and post-treatment changes for each cognitive test. (h–n) Graphs showing pre-post treatment and changes for each cognitive test dividing patients considering their cognitive phenotypes based on the number of affected domains (preserved, single-domain, bi-domain, multi-domain).

SDMT: Symbol Digit Modalities Test; BVMT: Brief Visuospatial Memory Test; CVLT: California Verbal Learning Test; DKEFS: Delis-Kaplan Executive Function System; TOWAS: DKEFS tower test; VFLTC, DKEFS verbal fluency total correct.

Discussion

This study provides new insights into the underlying mechanisms responsible for cognitive rehabilitation outcomes in MS patients. In addition to previous predictors,[3,4] our results suggest that RRCR can be predicted from baseline cognitive impairment, both in terms of quantity (number of impaired domains) and quality (type of impairment).

MS patients characterized by a single-impairment cognitive phenotype are those who benefit most from cognitive rehabilitation, showing significantly better improvement than patients with more affected cognitive domains (i.e. multi-domain impairment). Moreover, the specific cognitive domain that is impaired at baseline is also of great importance: our data suggested that lower functioning in a specific cognitive test was associated with a greater improvement within that test. Specifically, we found a beneficial treatment effect on memory and executive abilities. Consequently, assessing executive function in addition to the domains commonly tested with neuropsychological batteries (i.e. BICAMS and Brief Repeatable Battery of Neuropsychological Tests) is recommended.

The interpretation of our results indicates that patients with mild cognitive alterations (single-domain impairment) benefit most from our rehabilitation program. On the other hand, cognitively preserved patients do not require to be rehabilitated (i.e. ceiling effect), while for patients more severely cognitively impaired, a restorative approach may come too late and could prove less effective than compensatory training.[10] The present study is an early explorative study considering cognitive phenotypes that supported our previous results,[3,4] although it should be replicated in a larger study.

These preliminary results highlighted the importance of an early neuropsychological assessment and monitoring to identify slight cognitive alterations before the impairment is excessively broad and hardly recoverable. This will help clinicians with the possibility to characterize patients in terms of their cognitive phenotypes and to provide prompt administration of the cognitive rehabilitation to maximize the response obtained after the training.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

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