Article

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- Short Research Note -

Cognitive reserve mitigates decline in executive functioning following hepatobiliary diseases

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Running Title: Cognitive Reserve and Hepatobiliary Diseases

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Abstract

The cognitive reserve hypothesis postulates that lifelong cognitive stimulation establishes a buffer that is instrumental for maintaining cognitive health. To examine this conceptual proposition in detail, we applied a novel, more general conceptual view including recent models of vulnerability and examined whether the longitudinal association between hepatobiliary diseases and later decline in executive functioning across six years varied by cognitive reserve. For this purpose, we investigated longitudinal data from 897 older individuals (M = 74.33 years) who were tested on the Trail Making Test (TMT) in two waves six years apart. Individuals reported information on key commonly-used indicators of lifelong cognitive reserve build-up (i.e., education, work, and leisure activity participation) and hepatobiliary diseases. Results revealed a significant interaction of hepatobiliary diseases with leisure activity participation on latent change in executive functioning. Specifically, only for individuals with little (but not for those with greater) leisure activity participation, hepatobiliary diseases significantly predicted a steeper decline in executive functioning over six years (i.e., increases in TMT finishing time). In conclusion, the unfavorable aftereffects of hepatobiliary diseases on later decline in executive functioning seem to be mitigated in individuals who have built up greater cognitive reserve via leisure activity participation during their life.

Keywords: decline in executive functioning; cognitive reserve; hepatobiliary diseases; vulnerability; leisure activities; longitudinal study

Introduction

Because of the demographic changes, with progressively more individuals attaining a relatively old age, but also an increase of those suffering from cognitive impairments, the maintenance of cognitive health in late adulthood implies one of the biggest challenges in this century (Suzman, Beard, Boerma, & Chatterji, 2015). In this respect, cognitive reserve is an important factor (Stern, 2012). In general, the cognitive reserve hypothesis was initially developed to explain individual differences in cognitive health during aging and neurodegenerative diseases. Specifically, it postulates that lifelong cognitive stimulation establishes a buffer that is instrumental for dealing with brain alterations in order to maintain cognitive health (Stern, 2012). Commonly-used indicators of cognitive reserve are education, cognitively demanding work, and leisure activity participation during individuals' life that contribute to the build-up of cognitive reserve (Stern, 2012). These cognitive-reserve indicators are for instance associated with better executive functioning in healthy older individuals (Opdebeeck, Martyr, & Clare, 2016; Wang et al., 2013).

Cognitive reserve could be particularly important when faced with chronic health issues that affect cognitive functioning. For instance, hepatobiliary diseases (such as hepatitis, cirrhosis, cholelithiasis, cholecystitis, and cholangitis) are associated with an increased risk of cognitive dysfunction (Carvalho et al., 2017; Nardelli, Gioia, Faccioli, Riggio, & Ridola, 2019; Perry, Hilsabeck, & Hassanein, 2008). Applying a more general conceptual view including recent models of vulnerability (Cullati, Kliegel, & Widmer, 2018; Spini, Bernardi, & Oris, 2017) and cognitive reserve (Stern, 2012), we postulate that individuals who have built up less cognitive reserve during their life are more vulnerable to disease-related impairments in executive functioning. In line with this conceptual perspective, recent cross-sectional studies showed that cognitive

reserve seems to mitigate the negative cognitive aftereffects of metabolic disorders such as unfavorable blood fat level and hypertension (Ihle, Gouveia et al., 2018; Ihle et al., 2017). Moreover, with respect to hepatobiliary diseases, first studies indicated that cognitive reserve could perhaps help to cope with cognitive impairments associated with e.g. hepatitis C (Bieliauskas et al., 2007; Sakamoto et al., 2013). Yet, evidence has been so far only cross-sectional. Specifically, to the very best of our knowledge, there are no longitudinal examinations so far concerning the influence of cognitive reserve in mitigating the long-term aftereffects of hepatobiliary diseases on decline in executive functioning across a wider time frame. To address this major open issue in prior research, we examined whether the longitudinal association between hepatobiliary diseases and later decline in executive functioning across six years as indicated by performance changes in the Trail Making Test (TMT) varied by key commonly-used indicators of lifelong cognitive reserve build-up (i.e., education, cognitive demand of work, and leisure activity participation).

Materials and Methods

Participants

We analyzed data from 897 individuals who took part in the two waves of the Vivre-Leben-Vivere (VLV) survey (Ihle, Zuber et al., 2019; Ludwig, Cavalli, & Oris, 2014). Respondents were first tested in 2011 (Wave 1; W1) and again in 2017 (Wave 2; W2) using face-to-face computer-assisted personal interviewing (CAPI) and paper-pencil questionnaires. For further details concerning the rationale, design, recruitment, materials, and procedures of the VLV survey see (Ihle, Zuber et al., 2019; Ludwig et al., 2014). All individuals gave their written informed consent for inclusion in the study before data collection. The VLV study was conducted in accordance with the

Declaration of Helsinki, and the study protocol had been approved by the ethics commission of the Faculty of Psychology and Social Sciences of the University of Geneva (project identification codes: CE_FPSE_14.10.2010 and CE_FPSE_05.04.2017).

Materials

In both waves, we administered the Trail Making Test parts A and B (TMT A and TMT B, respectively; Reitan, 1958), which are commonly-used sensitive measures of inter-individual differences in intra-individual cognitive change (Chen et al., 2001). Individuals reported in W1 whether they suffered from hepatobiliary diseases such as hepatitis, cirrhosis, cholelithiasis, cholecystitis, and cholangitis. We used the Cognitive Reserve Index questionnaire (CRIq; Nucci, Mapelli, & Mondini, 2012) to assess indicators of cognitive reserve build-up during the lifespan in terms of education, cognitive demand of work, and leisure activity participation.

Statistical Analyses

We applied a latent change score modeling approach (McArdle, 2009) previously reported by our group (e.g., Ihle, Ghisletta et al., 2019; Ihle, Gouveia, Gouveia, Cheval et al., 2019; Ihle, Gouveia, Gouveia, Zuber, & Kliegel, 2019; Ihle, Gouveia, Gouveia, Zuber, Mella et al., 2019; Ihle et al., 2020), with latent executive functioning factors of TMT finishing time in W1 (constructed from TMT parts A and B in W1) and W2 (constructed from TMT parts A and B in W2) as well as a latent change in executive functioning variable concerning change in TMT finishing time from W1 to W2. We included the following covariates to predict latent change: hepatobiliary diseases in W1, the indicators of cognitive reserve (education, cognitive demand of work, and leisure activity participation), age in W1, sex, and the interactions of

hepatobiliary diseases in W1 with the indicators of cognitive reserve. We also included interrelations of all covariates to take the dependencies among them into account.

For model estimation, we used full information maximum likelihood. We evaluated model fit as follows: Given that with large study samples the χ^2 test often indicates a significant deviation of the model matrix from the covariance matrix despite good model fit (Hu & Bentler, 1999), we inspected several additional fit indices. Specifically, we used the following criteria: Comparative Fit Index (good models: *CFI* > .95), Incremental Fit Index (good models: *IFI* > .95), Root Mean Square Error of Approximation (good models: *RMSEA* < .06), and Standardized Root Mean Square Residual (good models: *SRMR* < .08; Hu & Bentler, 1999). We analyzed education, cognitive demand of work, leisure activity participation, and age as continuous variables. We standardized these covariates so that the reported raw estimates (*b*) can be interpreted in terms of *SD*s. We did not standardize finishing time in TMT A or TMT B so that the reported raw estimates can be interpreted in terms of seconds. Data are available online as supplemental material (Table S1).

Results

Descriptive statistics

Table 1 displays descriptive statistics of analyzed variables.

Latent change score modeling

The latent change score model provided a very good statistical account of the data (χ^2 = 29.52, *df* = 17, *p* = .030, *CFI* > .99, *IFI* > .99, *RMSEA* = .03, *SRMR* = .04).

Longer TMT finishing time in W1 (i.e., lower performance status in executive functioning) and greater past leisure activity participation during adulthood significantly predicted a smaller increase in TMT finishing time from W1 to W2 (i.e., smaller decline

in executive functioning; see Table 2). Older age in W1 significantly predicted a larger increase in TMT finishing time from W1 to W2 (i.e., steeper decline in executive functioning). Education, cognitive demand of work, sex, and hepatobiliary diseases per se did not predict changes in TMT finishing time. Notably, there was a significant interaction of hepatobiliary diseases with past leisure activity participation. To illustrate this interaction, we estimated in our latent change score model the longitudinal association between hepatobiliary diseases and changes in TMT finishing time at different values of the continuous variable leisure activity participation. Specifically, for individuals with little past leisure activity participation (-1 *SD*), hepatobiliary diseases in W1 significantly predicted a larger increase in TMT finishing time from W1 to W2 (i.e., steeper decline in executive functioning, $b = 15.91$, $p = .002$, corresponding $\beta = .16$). In contrast, for individuals with greater past leisure activity participation during adulthood (+1 *SD*), this longitudinal association between hepatobiliary diseases and steeper decline in executive functioning was no longer present (with even a marginal negative association pointing towards smaller decline in executive functioning; $b = -10.85$, $p = .084$, corresponding $\beta = -.11$; see Figure 1 for an illustration). Besides that, no other interactions of hepatobiliary diseases in W1 with the indicators of cognitive reserve on latent change in TMT finishing time were observed.

Discussion

As the first study on the potential influence of cognitive reserve for long-term decline in executive functioning following hepatobiliary diseases, our longitudinal findings have important implications. Applying latent change score modeling (to extract measurement-error variance) we revealed a considerable interaction of hepatobiliary diseases with past leisure activity participation on latent change in executive

functioning. In particular, for individuals with little past leisure activity participation, hepatobiliary diseases in the first wave of data collection predicted a steeper decline in executive functioning over six years (i.e., as indicated by increases in TMT finishing time). However, for individuals with greater past leisure activity participation during adulthood, there was no evidence of such longitudinal association between hepatobiliary diseases and steeper decline in executive functioning. These findings strengthen the proposition that cognitive reserve could perhaps help to mitigate the neuropsychological aftereffects of hepatobiliary diseases (Bieliauskas et al., 2007; Sakamoto et al.,2013). In this context, our longitudinal study advances prior cross-sectional studies with longitudinal data concerning decline in executive functioning across six years. Specifically, the longitudinal latent change score modeling approach applied in our analyses constitutes a highly important and innovative advancement in examining the influence of cognitive reserve in mitigating the long-term aftereffects of hepatobiliary diseases on decline in executive functioning across a wider time frame.

From a more general conceptual view, our findings are in line with postulations of recent models of vulnerability (Cullati et al., 2018; Spini et al., 2017) and cognitive reserve (Stern, 2012) and further confirm our conceptual perspective that certain individuals are more vulnerable (than other, less vulnerable ones) to impairments in executive functioning because of insufficient cognitive reserve built up during their life course that therefore exposes those vulnerable individuals to an increased strain to manage threatening situations (such as suffering from a chronic disease). In this regard, we disentangled the different contributions to cognitive reserve build-up during the individuals' lifespan and found that leisure activity participation had the major influence in this context (contrary to education and cognitive demand of work). These observations are in accordance with evidence indicating that leisure activity

participation makes a major contribution to the build-up of cognitive reserve during adulthood and shows associations with better performance and reduced decline in executive functioning in old age (Wang et al., 2013). Thereby, our study highlights leisure activity participation as critical cognitive-reserve indicator that will be later instrumental for enabling individuals to deal with the unfavorable cognitive aftereffects of hepatobiliary diseases.

With respect to the latter suggestions, we acknowledge that our correlative study cannot allow drawing causal inferences. Therefore, we are not able to entirely disentangle a potentially beneficial influence of leisure activity participation on later decline in executive functioning from substitute accounts such as older individuals possessing better executive functioning might pursue an active lifestyle. However, most importantly, our investigations based on latent longitudinal change scores in executive functioning and considered executive functioning level in the first assessment wave. Our measure of past leisure activity participation concerned individuals' entire adulthood, i.e. a timespan covering many decades before the examined outcome variables. Therefore, it is less likely that the association between past leisure activity participation and a subsequently smaller decline in executive functioning found in our study is attributable to individuals with reduced leisure activity participation as a consequence of decline in executive functioning. We further acknowledge that in our study hepatobiliary diseases based on self-reports. Future longitudinal studies will have to include a more detailed clinical evaluation. Furthermore, we acknowledge that another limitation of our study concerns the relatively brief assessment of executive functioning. Therefore, future longitudinal studies might examine whether the observed pattern of results applies also to a broader set of cognitive domains such as working memory and episodic memory (besides a wider range of executive function tasks).

Conclusions

Our findings suggest that the unfavorable aftereffects of hepatobiliary diseases on later decline in executive functioning could perhaps be mitigated in individuals who have built up greater cognitive reserve via leisure activity participation during their life. Our longitudinal study is of major importance for identifying possible intervention targets and health policies aiming at tackling vulnerabilities in health and their consequences. In this regard, particularly a lifelong stimulating activity participation should be promoted for building up cognitive reserve in order to reduce vulnerability in old age and support the maintenance of executive functioning following hepatobiliary diseases.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Table 1

Descriptive statistics of analyzed variables

Variable	***M* (*SD*) / sample proportions**
TMT A finishing time (W1) {seconds}	55.23 (24.40)
TMT A finishing time (W2) {seconds}	56.03 (24.37)
TMT B finishing time (W1) {seconds}	115.13 (44.80)
TMT B finishing time (W2) {seconds}	108.90 (45.40)
Hepatobiliary diseases (W1)	no: 97.3% yes: 2.7%
Education {CRIq score}	14.69 (5.35)
Cognitive demand of work {CRIq score}	114.95 (62.94)
Leisure activity participation {CRIq score}	446.45 (128.73)
Age (W1) {years}	74.33 (6.50)
Sex	men: 51.4% women: 48.6%

Note. Descriptive statistics for finishing time in Trail Making Test (TMT) parts A and B in Wave 1 (W1) and Wave 2 (W2), hepatobiliary diseases in W1, the indicators of cognitive reserve (education, cognitive demand of work, and leisure activity participation) examined with the Cognitive Reserve Index questionnaire (CRIq), age in W1, and sex with regard to means (standard deviations are given in parentheses) as well as sample proportions.

Table 2

Longitudinal predictions of latent change

	b	***β***
TMT finishing time (W1) {latent factor}	-0.39***	-.42
Hepatobiliary diseases (W1) {0 = no; 1 = yes}	2.56 ns	.03
Education	0.66 ns	.04
Cognitive demand of work	1.39 ns	.09
Leisure activity participation	-1.98**	-.12
Age (W1)	5.74***	.35
Sex {0 = men; 1 = women}	-0.29 ns	-.01
Interaction hepatobiliary diseases (W1) with leisure activity participation	-13.00***	-.16

Note. Parameter estimates of latent change score modeling for longitudinal predictions of change in Trail Making Test (TMT) finishing time from Wave 1 (W1) to Wave 2 (W2). Raw estimates *b* and corresponding standardized estimates *β* are given.

*** $p < .001$; ** $p < .01$; ns = non-significant, $p > .05$.

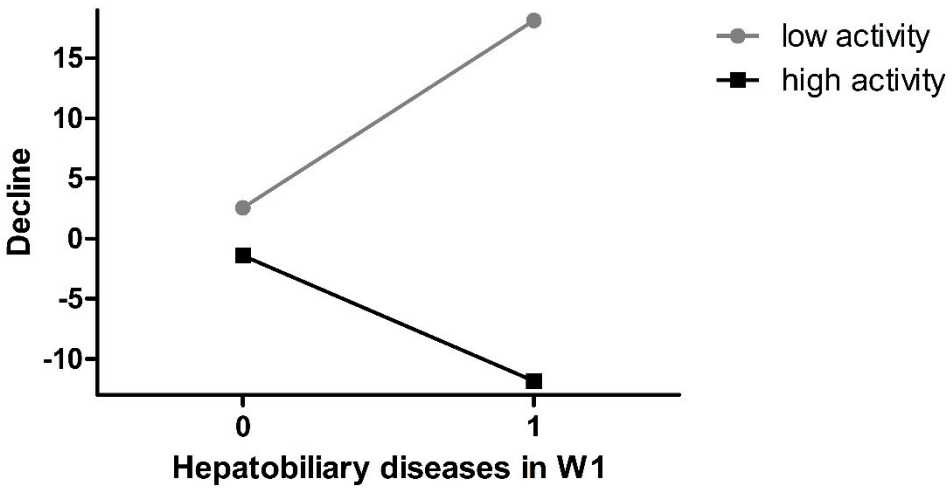

Figure 1. Illustration of the interaction of hepatobiliary diseases in Wave 1 (W1) with leisure activity participation on latent change. Estimated mean increase in Trail Making Test (TMT) finishing time from W1 to Wave 2 (W2) in seconds (i.e., decline in executive functioning) for individuals not suffering from hepatobiliary diseases (0) and individuals suffering from hepatobiliary diseases (1) as a function of past leisure activity participation (at a little and a great amount, i.e. -1 and +1 *SD*, respectively).