

Targeting mechanisms in cognitive training for neurodegenerative diseases

Annalena Venneri^{*}, Riccardo Manca, Linford Fernandes, Oliver Bandmann, Matteo De Marco

“Cognitive training” (CT) is a label used to describe paper-and-pen or computerized exercises designed to engage a desired set of mental skills for the purpose of enhancing neurocognitive functioning. Although the literature on the topic is considerably rich (on PubMed, for the sole 2018, the use of “cognitive training” as title keyword returns 123 results), very few studies pose the fundamental question: “How does CT work?”, or, more precisely, “Based on which computational mechanisms would engaging in CT result into meaningful changes in outcome measures?”. The overwhelming majority of the studies focus on treatment efficacy by modelling outcome measure(s) as a function of CT (e.g., an active CT condition versus an active control condition), but do not describe in detail the exact mechanistic reason why CT should have an effect in the first place (De Marco et al., 2014). Biological frameworks have been proposed [i.e., the hypothetical role played by neurotrophic factors, synaptic connections and neuroplasticity (Castells-Sánchez et al., 2019)] but these have been introduced as an *a posteriori* interpretation, not as a driving principle for the design of the exercises.

From a merely clinical viewpoint, biological explanations are not necessarily of central importance. In fact, it is normal for clinicians and clinical researchers to prioritize benefits to patients over the mechanistic description of the instruments (once these have proven feasible, ethical and safe). After all, by the same logic, we still have not been able to clarify with rigorous detail by which exact biophysical mechanisms certain popular neuromodulation techniques operate, such as transcranial direct-current stimulation (Pelletier and Cicchetti, 2014).

Identifying the mechanisms CT might rely on is of particular importance for the treatment of neurodegenerative diseases. This is by no means a trivial issue. A condition like Alzheimer’s disease, for instance, is characterized by multiple pathophysiological mechanisms and it is against these that CT would have to be conceptualized. A prevalent hallmark in neurodegenerative diseases is the accumulation of abnormal protein forms and aggregates (Bayer, 2015). It is not simple to align the mechanisms of CT to these processes, as there is a fundamental theoretical distance between peptidic and behavioral variables preventing us from drawing direct causative links. Reflecting on this apparent theoretical incompatibility, however, can be a productive exercise. In fact, it enables us to define a common ground on which both cellular

and peptidic as well as behavioral variables can be transposed and investigated. This is the level of the neural systems deputed to information processing, already identified by the Imaging Genetics framework as “*a more proximate biological link to genes*” and as “*an obligatory intermediate of cognition, behavior and emergent phenomenon*” (Mattay et al., 2008). It is at this level that CT can be devised as an instrument deputed to target a specific mechanism. The possibility of relying on cognitive operations to target the overall systems is also conveniently aligned with the use of neuroimaging as methodology to measure such systems. Techniques such as magnetic resonance imaging and positron emission tomography enable researchers to investigate properties of the brain throughout its entire topography. On this note, functional magnetic resonance imaging is particularly helpful because it allows the calculation of large-scale haemodynamic networks. This is particularly relevant for the study of neurodegeneration, because neurodegenerative diseases affect these networks with a large degree of selectivity (Seeley et al., 2009). As a result, focusing on whole-brain patterns of functional connectivity provides a theoretical ground on which disease mechanisms, training principles and test-retest outcome measurements are conveniently aligned (Figure 1).

Based on such alignment, we have proposed a CT hypothesis aimed at inducing synchronized activity of selected brain regions. Referring to Alzheimer’s disease as the diagnosis of interest, the underlying principle defining our hypothesis was that repeated task-related co-activation of multiple areas would result in increased resting-state functional connectivity among those areas (Martínez et al., 2013). On the basis that Alzheimer’s pathology selectively affects the brain’s default-mode network (Seeley et al., 2009; Pasquini et al., 2017), we designed a set of computerized exercises aimed at inducing co-activation of central hubs of this network. These exercises are centrally reliant on retrieval from semantic memory, but patients are also required to recruit a significant amount of executive resources in order to solve the tasks. The combined processing of semantic content, memory retrieval and executive control (each of which is supported by a specific theory-informed pattern of brain areas) is at the basis of the task-induced co-activation of multiple regions of the default-mode network including the hippocampus, lateral temporal cortex, posterior cingulate and medio-prefrontal cortex. After validating

this principle in a cohort of healthy older adults (De Marco et al., 2016), we found that this approach up-regulates functional connectivity of the default-mode network in patients with mild cognitive impairment and a working diagnosis of prodromal Alzheimer’s disease (De Marco et al., 2018), in favor of our hypothesis. In further support of the construct validity of our CT conceptualization, we also found that the presence of a high load of white-matter hyperintensities (small lesions that impair inter-neuronal connectivity) is associated with significantly fewer modifications of network connectivity after CT (Bentham et al., 2019). To corroborate the efficacy of our network-based CT in a completely different diagnostic scenario in which, however, mild cognitive impairment has also been linked to disruption of functional connectivity in the default-mode network (Hou et al., 2016), we ran a pilot study in a group of 23 patients diagnosed with Parkinson’s disease (PD) and mild cognitive impairment, on the basis that up-regulation of the default-mode network would also translate into cognitive improvements in this diagnostic group. Twelve of these patients with a diagnosis of PD and mild cognitive impairment underwent the network-based CT as described in our previous studies with healthy older adult and prodromal Alzheimer’s disease participants (De Marco et al., 2016, 2018; Bentham et al., 2019). The remaining patients with PD and mild cognitive impairment acted as controls as they followed a pathway of care as usual. These two groups were compared on behavioral outcome measures only, with assessments at baseline, after four weeks and at a longer-term follow-up, 6 months after baseline.

In support of our hypothesis, after 4 weeks of CT, improvement from baseline was observed across most cognitive tests for the treatment group (Additional Figure 1). Significant changes that survived correction for multiple comparisons, however, were only detected for the Semantic Fluency test ($P = 0.001$), the Scales for Outcomes of PD–Cognition ($P = 0.002$) and the Trail Making test - part A ($P = 0.003$). In contrast, the participants in the control group showed no significant changes in any of the neuropsychological tests. The improvements observed in the PD treatment group just after termination of the training (at 4 weeks) were not maintained after 6 months, but their scores remained higher than those recorded at baseline, suggesting time limited benefit in the absence of sustained stimulation of target mechanisms. Interestingly, in this group no significant improvements in the reaction times or accuracy scores were found over the course of the CT sessions, suggesting that the observed improvements in the group receiving CT were not dependent on improved motor performance.

Aside from the small sample size that prevents definite and generalizable conclusions on the effectiveness of this CT for patients with PD and mild cognitive impairment, major limitations are identified:

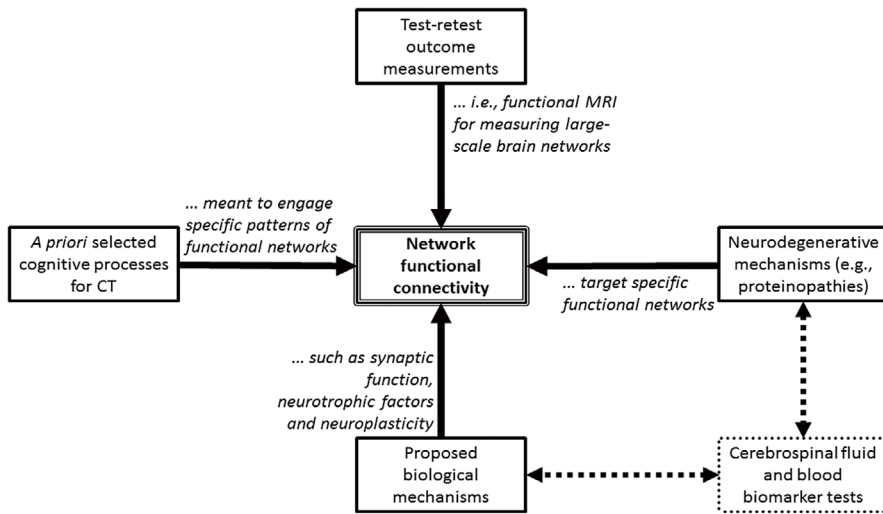


Figure 1 | Theoretical framework of mechanistic CT for neurodegenerative diseases.

Although the pathological processes of diseases such as Alzheimer's disease or frontotemporal lobar degeneration are normally defined at the cellular level (e.g., aberrant deposition of misfolded proteins, neural inflammation, impaired cellular metabolism), it is important to establish a theoretical alignment between disease and treatment mechanisms. This can be achieved by focusing on the large-scale brain systems, which have been proven to show direct connections with both disease mechanisms as well as neuropsychological functions that are at the basis of CT. Moreover, the focus on brain systems enables the alignment of test-retest outcome measures such as positron emission tomography or functional MRI (the latter allowing the direct measure of test-retest changes in whole-brain systemic patterns of functional connectivity). CT: Cognitive training.

first, the absence of MRI data limits our margin of interpretation in this specific diagnostic sample; second, and more in general, concurrent neurovascular factors may impact on mechanisms and treatment response. On this note, the inclusion of multiple MRI sequences in future investigations may support a more robust interpretation of findings.

In conclusion, these findings corroborate the evidence that mechanistic CT aimed at inducing changes in functional connectivity of neural systems is effective in supporting performance gains in the presence of neurodegeneration. Central to this framework is the identification of treatment mechanisms. Our proposition is that a network-based approach is suitable for aligning disease pathology, treatment mechanisms, cognitive functioning and test-retest outcomes on the common theoretical ground of neural systems. We argue that the definition of such strong theoretical rationale confers considerable advantage in comparison to more pragmatic clinical studies that are solely interested in the effect of CT and often conceive CT as a simple "symptomatic" form of treatment (i.e., "memory difficulties, then memory exercises"). Non-pharmacological interventions can be a powerful instrument in the treatment of neurodegenerative diseases, yet are often tacitly regarded as subsidiary, auxiliary tools to be used alongside a main recognized form of treatment that usually consists of one or more medications. Pharmacological treatments are seen as the "natural" avenue to counteract cognitive decline in neurodegenerative diseases because they target disease mechanisms in a direct way, i.e., there is a direct causative link between

the drug and the brain. In order to see CT approaches become a primary therapeutic option it is necessary to follow the same rationale and define CT approaches that address specific disease mechanisms either directly or indirectly. For this reason, we argue that a transition from a symptom-driven to a mechanism-driven approach to CT will enable this underdeveloped field of research to progress and become central for the development of treatment options against cognitive decline due to neurodegenerative diseases.

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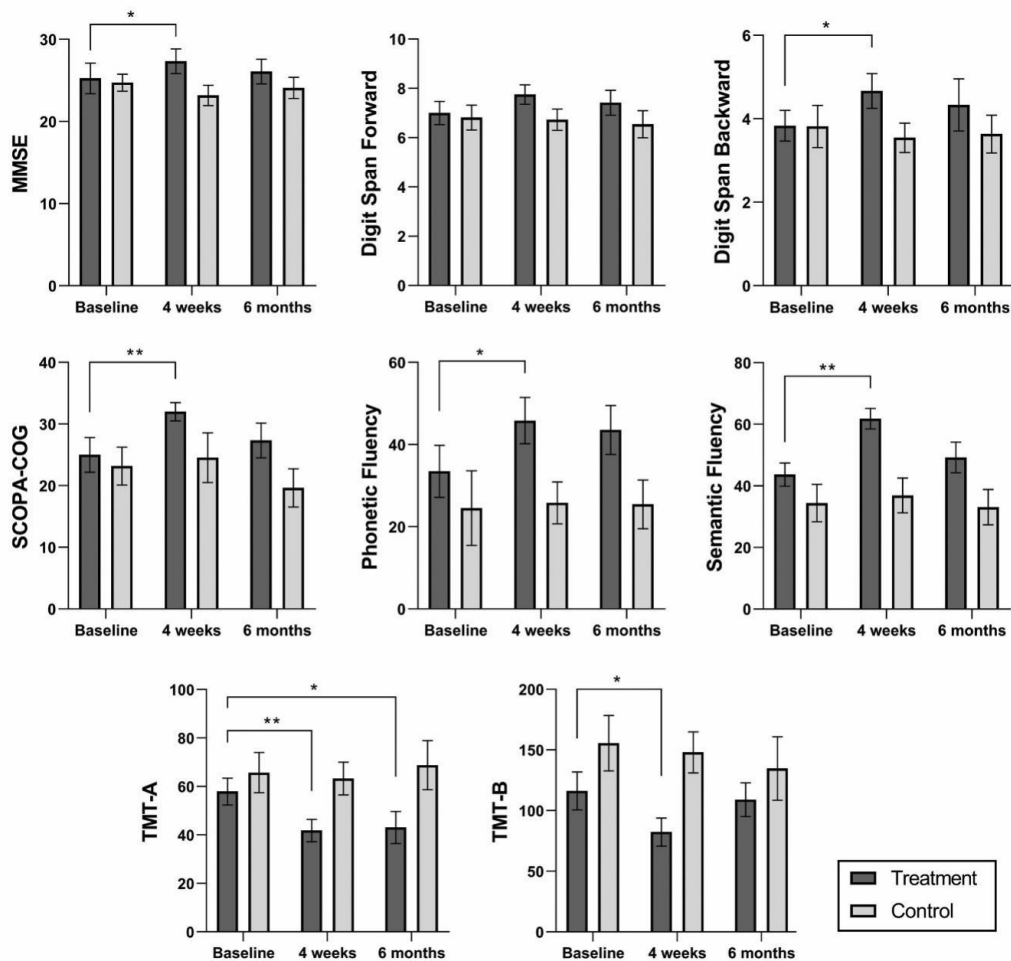
Additional file 1: Open peer review reports 1 and 2.

Additional Figure 1: Changes in cognitive performance in the treatment and control PD groups.

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Additional Figure 1 Changes in cognitive performance treatment and control PD groups

Mean cognitive scores (95% CI) at baseline, 4 weeks and 6 months in 23 patients with Parkinson's disease with mild cognitive impairment allocated to two groups: treatment ($n = 12$), those who underwent CT, and control ($n = 11$), those who did not undergo CT. Significant ANOVA results ($*P < 0.05$, $**P < 0.00625$) are shown for the comparisons between scores at baseline, at 4 week- and at 6 month- follow-ups. MMSE: Mini Mental State Examination, SCOPA-COG: Scales for Outcomes of PD – Cognition, TMT-A/B: Trail Making test – part A and B. Candidate participants with a working diagnosis of PD were recruited from the movement disorder clinic at the Royal Hallamshire Hospital, Sheffield, UK. All participants fulfilled PD Society Brain Bank Criteria, were on stable treatment regime, reported subjective cognitive impairment and had a Mini Mental State Examination score between 23 and 27. Exclusion criteria consisted of the presence of concomitant diagnostic elements other than a diagnosis of PD that could have otherwise accounted for the presence of neurological symptoms. The study received ethical approval from the Regional Ethics Committee of Yorkshire and Humber (Ref No: 12/YH/0474). All participants provided written informed consent. All study procedures were carried out in compliance with the 1964 Declaration of Helsinki and its subsequent amendments. At baseline, participants underwent a comprehensive cognitive assessment in line with the Movement Disorder Society Task Force recommendations. The threshold of statistical significance was set at 0.05 and the Bonferroni correction was used to account for multiple comparisons ($P = 0.05/8 = 0.00625$). The two groups (CT and control condition, respectively) did not differ in age (73.0 ± 7.68 vs. 75.7 ± 4.73), years of education (18.5 ± 3.09 vs. 17.7 ± 3.13), years of disease duration (11.1 ± 3.34 vs. 12.3 ± 6.12), MMSE (25 ± 1.85 vs. 25 ± 1.56) and SCOPA-COG (25 ± 4.45 vs. 23 ± 4.58). All showed objective mild cognitive impairment when tested with neuropsychological assessment.