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Brief Communication

Computational Modeling of Neuropsychological Test Performance to Disentangle Impaired Cognitive Processes in Cancer Patients

Joost A. Agelink van Rentergem, PhD,[1,2,*] Ivar E. Vermeulen, PhD,[3] Philippe R. Lee Meeuw Kjoe, MSc,[2] Sanne B. Schagen, MSc,[1,2]

[1]Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands;, [2]Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands; and [3]Department of Communication Science, VU University Amsterdam, Amsterdam, The Netherlands

[*]**Correspondence to:** Joost Agelink van Rentergem, PhD, Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, H8.014, Amsterdam, 1066CX, Netherlands (e-mail: j.agelink@nki.nl).

Abstract

There is a need to better identify impaired cognitive processes to increase our understanding of cognitive dysfunction caused by cancer and cancer treatment and to improve interventions. The Trail Making Test is frequently used for evaluating information-processing speed (part A) and executive function (part B), but interpretation of its outcomes is challenging because performance depends on many cognitive processes. To disentangle processes, we collected high-resolution data from 192 non–central nervous system cancer patients who received systemic therapy and 192 cancer-free control participants and fitted a Shifted-Wald computational model. Results show that cancer patients were more cautious than controls (Cohen $d = 0.16$). Patients were cognitively slower than controls when the task required task switching (Cohen $d = 0.16$). Our results support the idea that cancer and cancer treatment accelerate cognitive aging. Our approach allows more precise assessment of cognitive dysfunction in cancer patients and can be extended to other instruments and patient populations.

Neuropsychological assessment is a key component of care for cancer patients facing cognitive dysfunction. The choice of an intervention to diminish cognitive problems is based on neuropsychological assessment (1,2), so care can be improved by enhancing precision of assessment instruments. One of the most used tests (3,4), and part of the core battery recommended by the International Cognition and Cancer Task Force (5), is the Trail Making Test (TMT) (6). Cancer and cancer treatment affect performance on the TMT, although results are mixed (7–9), and impairments may differ between patients (10). The TMT has two parts. Part A requires patients to connect circles labeled 1 and 2, 2 and 3, and so on. Part B requires connecting circles labeled 1 and A, A and 2, 2 and B, and so on (11). Traditional outcomes include the time to complete part A and part B, and the ratio or difference between the two.

Although the primary goal of part A is to measure information-processing speed, individual differences in performance can also reflect differences in motor slowing (12), numerical ability, decisiveness, and attention (6). Although the primary goal of part B is to measure executive functioning, differences in performance can also reflect differences in working memory, alphabetism, motor slowing, numerical ability, decisiveness, and attention (13). The influence of these secondary processes decreases the interpretability and diagnosticity of test results (14). From traditional outcomes, primary and secondary processes cannot be disentangled.

To disentangle cognitive processes, we obtained data (15,16) using a computerized version of the TMT. This test is part of the Amsterdam Cognition Scan, a test battery designed to be completed without supervision and on the participant's own computer (15). The Amsterdam Cognition Scan stores high-resolution data, that is, per mouse click, allowing more sophisticated analyses of processes underlying participants' performance. Participants included 192 patients (112 women, mean [SD] age: 52.4 [11.9] years) with non–central nervous system (non-CNS) cancer who received systemic therapy (chemotherapy, hormonal therapy, or immunotherapy, or a combination) and 192 controls (123 women, mean [SD] age = 51.1 [11.4] years) without a history of cancer and recruited via participants after outlier removal and matching on age (see Supplementary Methods, available online). The institutional review board of the Netherlands Cancer Institute approved the study. Written informed consent was obtained from all participants before the assessments. As reaction times, the time to transition from one

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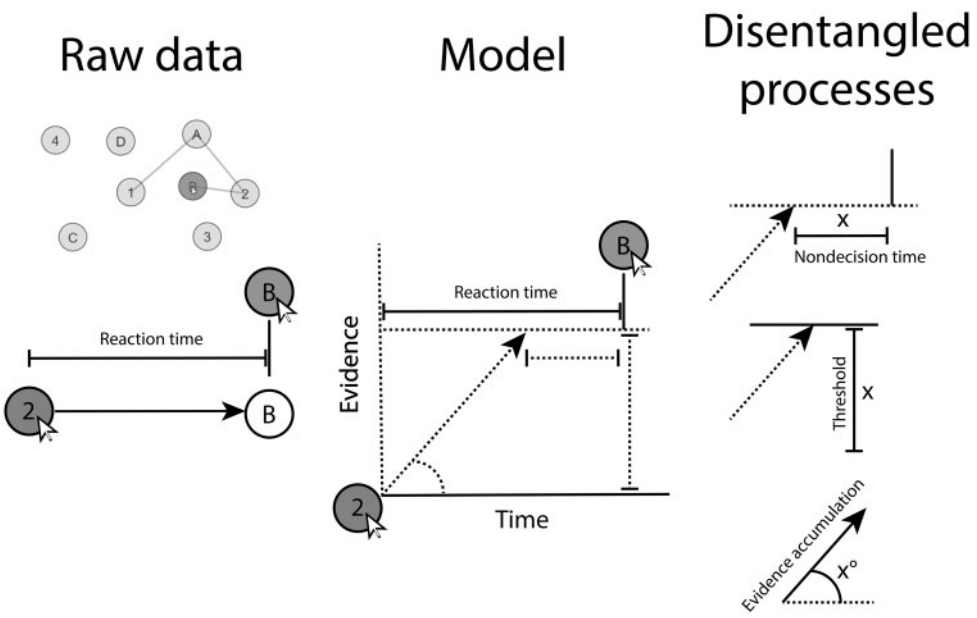

Figure 1. Illustration of how raw reaction times are decomposed into three cognitive processes in the Shifted-Wald model.

circle to the next was used, resulting in 24 reaction times per part and 48 reaction times in total per person (18 432 reaction times overall).

We fitted a hierarchical Bayesian cognitive model (17). Hierarchical Bayesian models provide the optimal balance between estimating parameters at the group level and estimating interindividual heterogeneity (18) and are well suited for cognitive modeling (19). Cognitive models allow disentanglement of processes by requiring the specification of a mathematical model and its assumptions (20). We used a Shifted-Wald model to relate the time participants required to connect circles to three parameters: evidence accumulation, threshold, and nondecision time (21, 22).

Each parameter defines an aspect of the response time distribution (21) and represents a distinct process [see Figure 1 for a review (23) and Supplementary Methods, available online, for further explanation]. Evidence accumulation can be interpreted as cognitive speed. If the evidence accumulation parameter is high, participants gather evidence quickly and respond quickly. The threshold can be interpreted as response caution. If the threshold is low, participants require little evidence and respond quickly. Nondecision time can be interpreted as time required for noncognitive parts of the task. If nondecision time is low, participants waste little time on noncognitive tasks, such as physically moving and clicking the mouse, and respond quickly.

We fitted the model in Stan (24) (see Supplementary Methods, available online, for model code and convergence diagnostics). For each parameter and comparison, we computed the 95% highest posterior density interval (25,26) to quantify statistical significance, signifying an α level of .05, and two-sided testing. Findings are depicted in Figure 2 (numbers in Supplementary Tables, available online, observed and estimated distributions to assess model fit in Supplementary Figure 10, available online).

Evidence accumulation was slower for patients than for controls during part B but not during part A; the task that requires switching between letters and numbers is more difficult for cancer patients than for controls. Thresholds were higher for patients than for controls for both parts A and B, indicating that cancer patients are more cautious. Patients and controls did not differ in time needed to complete noncognitive parts of the test. This suggests that motor speed is intact in cancer patients.

The observed differences between patients and controls on evidence accumulation and threshold were both small ($d = 0.16$). These differences will most probably not be of immediate concern to patients undergoing chemotherapy. Instead, they inform us on the mechanisms of cognitive dysfunction. Because these mechanisms can affect performance on more domains than the TMT measures, the impact of these differences may be more widespread than the small effect sizes initially suggest.

Cancer patients showed more caution in their responses. This "conservative" response is frequently observed when comparing older and younger patients using the Shifted-Wald Model (27) and related models and tasks (28,29) and is associated with age-related reductions in white matter integrity between cortex and striatum (29). Second, patients' cognitive speed was slower when the task required task switching. Age-related slowing in task switching accompanies decreases in frontoparietal white matter integrity (30). White matter integrity is found to be decreased in cancer patients as well (31). That the pattern of cognitive results converges between cancer patients and aging participants supports the idea that cancer treatment may accelerate cognitive aging (32–34).

The Shifted-Wald model can be extended to other timed tasks and is applicable beyond non-CNS cancer to psychiatric and neurological conditions associated with cognitive decline. A potential limitation of our approach is the assumption that reaction times are homogeneously composed of the same three processes. This assumption may be violated in participants who strategically pause between circles to map out the next clicks. Although such strategies are not obvious given task instructions, a modeling approach that statistically separates strategies may be a fruitful extension (35).

Currently, behavioral and pharmacological interventions for cognitive decline in cancer patients lean on findings from outside the non-CNS cancer literature, because information on the

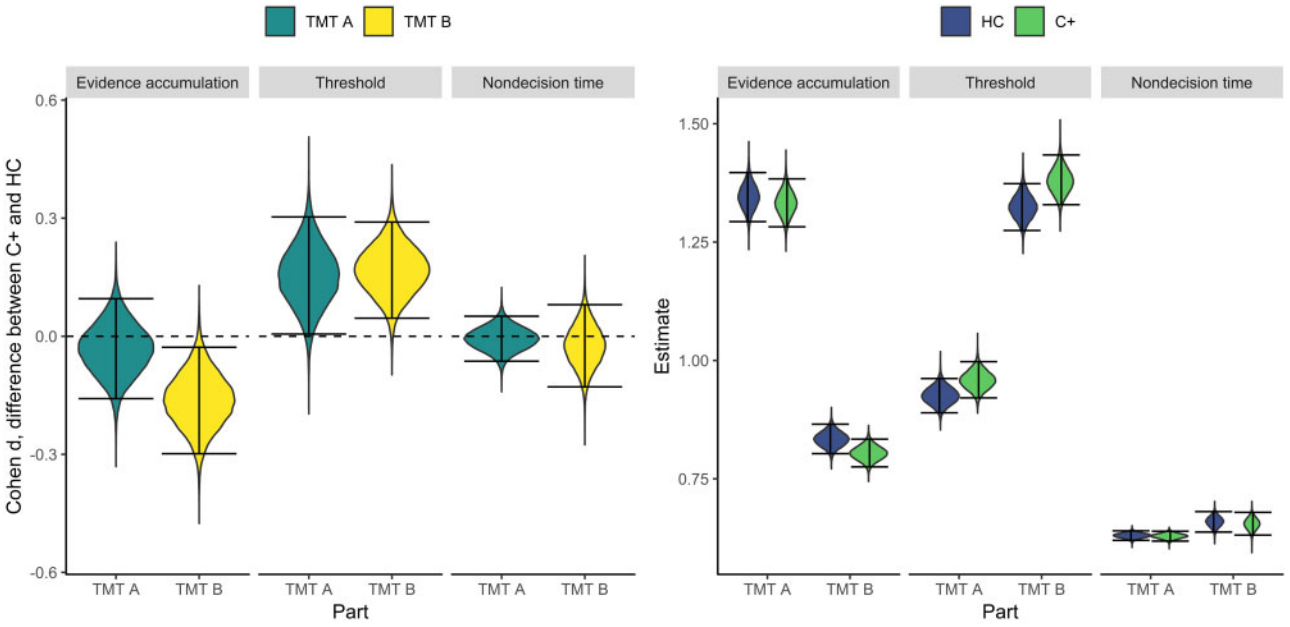

Figure 2. Distributions of effect sizes and parameter estimates on three parameters and parts A and B of the TMT. Intervals denote 95% highest posterior density intervals. C+ = non–central nervous system cancer patients; HC = controls; TMT = Trail Making Test.

mechanistic nature of cognitive dysfunction in cancer patients is sparse. More such knowledge improves information for patients and caretakers on the cognitive phenotype and will guide the search for more effective interventions that target the basis of decline.

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