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Attention network test: Assessment of cognitive function in chronic fatigue syndrome

Fumiharu Togo[1]*, Gudrun Lange[2,3], Benjamin H. Natelson[4] and Karen S. Quigley[3,5]

[1]Educational Physiology Laboratory, Graduate School of Education, University of Tokyo, Japan
[2]Department of Physical Medicine and Rehabilitation, UMD-New Jersey Medical School, Newark, New Jersey, USA
[3]Department of Veteran Affairs, New Jersey Health Care System, East Orange, New Jersey, USA
[4]Pain and Fatigue Study Center, Beth Israel Medical Center and Albert Einstein Medical Center, New York City, New York, USA
[5]Interdisciplinary Affective Science Laboratory, Northeastern University, Boston, Massachusetts, USA

Information processing difficulties are common in patients with chronic fatigue syndrome (CFS). It has been shown that the time it takes to process a complex cognitive task, rather than error rate, may be the critical variable underlying CFS patients' cognitive complaints. The Attention Network Task (ANT) developed by Fan and colleagues may be of clinical utility to assess cognitive function in CFS, because it allows for simultaneous assessment of mental response speed, also called information processing speed, and error rate under three conditions challenging the attention system. Comparison of data from two groups of CFS patients (those with and without comorbid major depressive disorder; n = 19 and 22, respectively) to controls (n = 29) consistently showed that error rates did not differ among groups across conditions, but speed of information processing did. Processing time was prolonged in both CFS groups and most significantly affected in response to the most complex task conditions. For simpler tasks, processing time was only prolonged in CFS participants with depression. The data suggest that the ANT may be a task that could be used clinically to assess information processing deficits in individuals with CFS.

Chronic fatigue syndrome (CFS) is a medically unexplained illness characterized by persistent or relapsing fatigue lasting at least 6 months and producing substantial interference with normal activities accompanied by rheumatological, infectious and neuropsychiatric complaints of similar duration (Fukuda *et al.*, 1994). Prominent among these are cognitive difficulties including problems with information processing, learning, memory, and problem-solving (Deluca, Johnson, & Natelson, 1993; Short, McCabe, & Tooley, 2002; Tiersky, Johnson, Lange, Natelson, & Deluca, 1997; Wearden & Appleby,

*Correspondence should be addressed to Fumiharu Togo, Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan (email: tougou@p.u-tokyo.ac.jp).

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1997). Although impairments have been found in a variety of cognitive domains, the most robust findings in individuals with CFS are inefficient, slowed information processing in the verbal (Deluca, Johnson, Ellis, & Natelson, 1997) as well as visual domains (Deluca *et al.*, 2004). Information processing is a basic cognitive component providing the underpinning for many other higher order cognitive functions including learning, memory, and problem-solving. As speed of information processing decreases, the amount of information held at any one time in working memory, which stores and manipulates information, decreases (Wilhelm & Oberauer, 2006). Reduced working memory capacity can in turn affect an individual's ability to set decision-making priorities, resolve conflicts, inhibit irrelevant information, and to make decisions appropriately, smoothly, efficiently, and cumulatively. These functions are subsumed under the term executive function, useful and often necessary for multitasking. Many individuals with CFS are challenged by multiple and competing input – leading to difficulties with multitasking especially under conditions of increasing complexity when there is a need to screen out irrelevant information.

The development of the Attention Network Task (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) is based on a well-developed neural network model of the human attention system (Fan *et al.*, 2002; Posner & Petersen, 1990). The ANT combines a cued reaction time (RT) task (Posner, 1980) and a flanker task (Eriksen & Eriksen, 1974) and was developed to assess the operation of the attention system across three kinds of attention processing: alerting, orienting, and executive control (Posner & Petersen, 1990). The alerting condition of the ANT reflects the extent to which there is a benefit of temporal cueing to maintain cognitive vigilance. To assess orienting, a spatial cue is used before onset of the primary stimulus that reveals the efficiency with which subsequent targets can be located in space. Executive function is assessed by using peripheral or flanking arrows incongruent with a central target arrow that requires quick decision-making, response coordination, and execution. We hypothesized that individuals with CFS would have significantly more difficulties (i.e., perform significantly more slowly) on the executive function component of the ANT when controlling for generalized slowing (measured using a simple RT task) consistent with previous findings (Deluca *et al.*, 2004), using a different set of cognitive performance measures. In an earlier anatomical neuroimaging study, Lange *et al.* (1999) found CFS patients to have the most abnormalities in the frontal lobes – the region of the brain which includes a part of the executive control network. A functional neuroimaging study showed that activations of the alerting, orienting, and executive control networks were associated with the thalamic activations, parietal activations, and anterior cingulate cortex activations, respectively (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Therefore, we also hypothesized that individuals with CFS would not have difficulties on the alerting and orienting component of the ANT when controlling for generalized slowing.

Methods

Study participants

We recruited 41 individuals with CFS from a tertiary clinical care practice and 29 healthy volunteers via referral from patients or by their responding to advertisements in local publications; the 54 female and 16 male participants ranged from 20 to 64 years. All participants were screened by self-report for the following inclusion criteria by the study physician (BHN): (1) no history of neurological disorder; (2) no history of major neuropsychiatric disorder (bipolar disorder, psychotic depression, schizophrenia, dementia) or alcohol or drug abuse based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) criteria; (3) no history of loss of consciousness of 5 min or more; (4) no use of medications known to affect cognition (e.g., benzodiazepines, prednisone). Patients fulfilled the 1994 CFS case definition and had no medical explanation for their symptoms based on history, physical examination, and blood tests (Fukuda *et al.*, 1994).

Based on the clinical evaluation, healthy controls did not have current major depressive disorder while 22 individuals with CFS did. CFS participants with depression were all taking therapeutic doses of antidepressant medications, and some were taking additional medication for sleep and for pain (e.g., low dose tricyclics plus antiepileptic medications). CFS participants without comorbid depression usually were taking some medication for sleep and some were on pain management regimens similar to those in the depressed subgroup. All study participants reported normal or corrected-to-normal vision. All participants provided informed consent to participate in this research as approved by the UMDNJ-NJMS Institutional Review Board.

Simple reaction time task

Participants were instructed to press a key on a computer keyboard as quickly as possible once a stimulus – a black circle – appeared on a computer screen. The black circle was centrally displayed against a grey background. Each trial lasted for a total of 4,000 ms and consisted of three events: a fixation period of random duration (100–2,000 ms), the stimulus presentation period lasting until the participant pressed the response key (RT), but not to exceed 2,000 ms, and a post-stimulus period that varied based on the duration of the fixation period plus the participant's RT. After this interval, a fixation period (100–2,000 ms) for the next trial began (2,000–3,900 ms after the previous stimulus presented) and the next stimulus was presented. Therefore, an inter-stimulus interval ranged from 2,100 to 5,900 ms. Performance on the simple RT task reflected motor speed. Following a practice session of 10 trials, participants completed an experimental block of 20 trials of the simple RT task from which we determined the median RT.

Attention Network Task

Figure 1 depicts the details of the task. During the cued RT conditions, one of four cue types was provided: no cue, a centre cue, a double cue, or a spatial cue to alert the participant to the possible location of an array of arrows (the flanker condition) that would subsequently appear on the screen. Next, an array of stimuli was presented consisting of a central stimulus (an arrow pointing either left or right) and flankers that were either congruent (two flanking arrows on either side of the central arrow all pointing in the same direction as the central arrow), incongruent (a set of flanking arrows which pointed in the opposite direction of the central arrow), or neutral (two horizontal lines on either side of the central arrow). Compared to the congruent flankers, the incongruent flankers introduce conflict likely to result in longer RTs (i.e., slower information processing speed) and the potential for reduced response accuracy. Participants were instructed to respond as quickly as possible by indicating whether the central arrow pointed to the left or right using specific keys on a keyboard for each choice (the letter Z to indicate left and the letter M for right). Figure 1 illustrates the order in which stimuli were presented beginning with

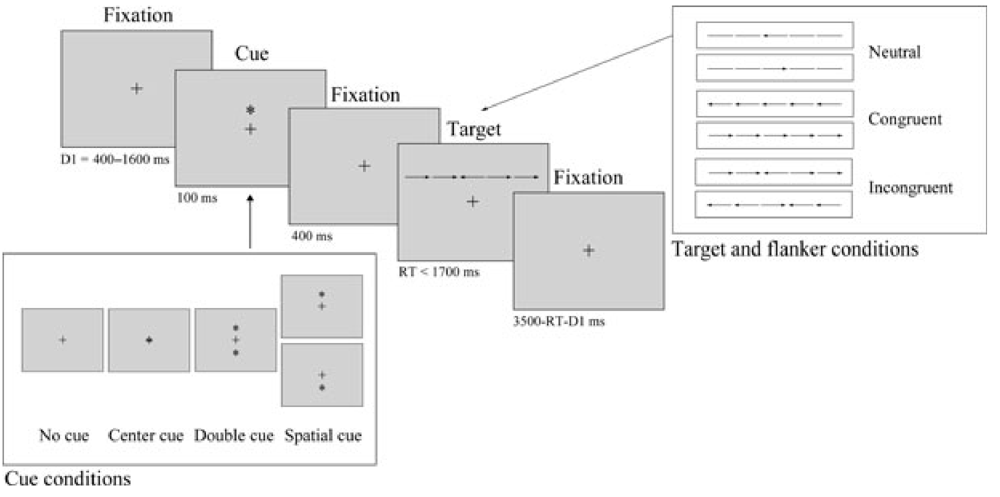

Figure 1. Schematic depiction of the Attention Network Task. RT = reaction time.

a fixation stimulus, followed by one of four possible cues, another fixation stimulus, the flanker condition, and finally a fixation point.

Each session began with a 24-trial practice block during which feedback was provided for each trial to ensure comprehension of task demands. Immediately following the practice session, participants were administered three experimental blocks of trials without feedback. Each experimental block consisted of 96 trials (4 cue conditions [no cue, centre cue, double cue, spatial cue] × 2 target locations [above or below fixation] × 2 central arrow directions [left- or right-pointing] × 3 flanker conditions [neutral, congruent, incongruent] × 2 repetitions). Trials were presented in random order. Each experimental block of trials took approximately 6 min and up to 2 min was allowed for rest between blocks of trials.

We computed the median RT for correct trials as a function of cue or flanker condition for each participant. To calculate the effect of an alerting cue on response times, the median RT of the double cue trials was subtracted from the median RT of the no cue trials, because these conditions differed only in terms of whether or not the participant was alerted before the array of flankers appeared (Fan *et al.*, 2002). To calculate the orienting effect, the median RT of the spatial cue trials was subtracted from that of the central cue trials (Fan *et al.*, 2002). Spatial cues reliably provide information about where the stimulus will appear whereas central cues do not, thus providing a spatial cue that can orient the person to the subsequent location of the flanker array. Finally, to calculate the executive function effect, the median RT of the congruent flanker conditions was subtracted from the median RT of the incongruent flanker conditions (Fan *et al.*, 2002).

Statistical analyses

Information processing speed was calculated by subtracting the median simple RT (i.e., reflecting motor response time) from each cue or flanker condition RT. Differences in information processing speed and error rates between groups were assessed using two-factor (groups and cue or flanker conditions) repeated-measures ANOVAs. Differences in simple RT, alerting, orienting, and executive function among groups also were assessed using ANOVAs. *Post-hoc* analyses used Tukey's studentized range tests to compare means across groups and conditions. Effects were considered statistically significant at $p < .05$ or better.

Results

Age and gender did not differ significantly among healthy controls, CFS alone, and CFS with depression, mean ± *SD*: 44 ± 8, 43 ± 10, and 47 ± 8 years, respectively; $F(2, 67) = 1.33$, $p > .05$. There was a significant effect of group on median simple RT (i.e., motor speed), $F(2, 67) = 3.16$, $p < .05$. *Post-hoc* analysis revealed that median simple RT was significantly ($p < .05$) longer for CFS patients with depression (416 ± 145 ms [*SD*]) than for healthy controls (339 ± 80 ms). There was no difference ($p > .05$) in median simple RT between healthy controls and the CFS alone group (388 ± 114 ms).

There was a significant effect of cue condition on information processing speed, $F(3, 201) = 75.15$, $p < .05$. Information processing speed (i.e., RT for correct trials for each cue condition after subtracting the median simple RT) increased for all groups as fewer cues to the timing or location of the appearance of the flankers were presented (Figure 2a). There was a significant effect of group on information processing speed,

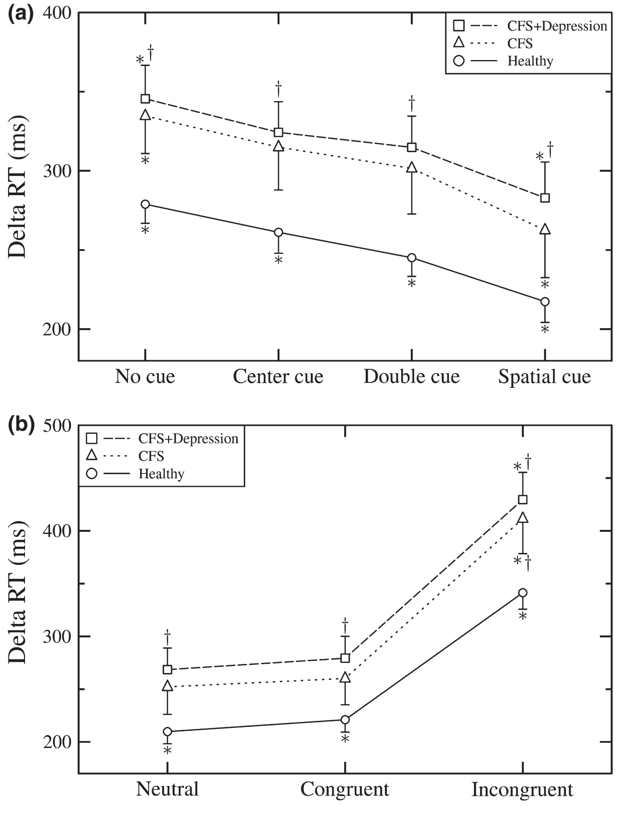

Figure 2. Delta reaction time (RT) calculated by subtracting median simple RT from median RT for correct trials as a function of (a) cue and (b) flanker conditions for healthy controls, the chronic fatigue syndrome (CFS) alone group, and the CFS with depression group. Values are means ± SE.
*Significantly different from other conditions within a group ($p < .05$); †Significantly different from healthy controls ($p < .05$).

$F(2, 67) = 3.74, p < .05$. No differences existed between CFS groups for any of the cued RT task conditions ($p > .05$). Compared to healthy controls, the CFS with depression group had significantly ($p < .05$) slower processing speed in all conditions whereas the CFS alone group did not ($p > .05$) (Figure 2a). The trajectory of response, however, was similar among groups, which produced similar latencies in the alerting, healthy controls: 33 ± 24 ms; CFS alone: 27 ± 54 ms; CFS with depression: 33 ± 43 ms; $F(2, 67) = 0.17$, $p > .05$, or orienting, healthy controls: 48 ± 37 ms; CFS alone: 51 ± 43 ms; CFS with depression: 43 ± 40 ms; $F(2, 67) = 0.26, p > .05$, conditions among groups.

Error rates for each flanker condition were similar among groups (mean ± *SD*: 0.97 ± 1.20%, 0.66 ± 0.79% & 1.00 ± 2.10% in the neutral condition, 0.41 ± 0.66%, 0.38 ± 0.62% & 1.28 ± 2.38% in the congruent condition, and 2.68 ± 4.58%, 1.48 ± 2.44% & 3.84 ± 8.05% in the incongruent condition for healthy, CFS alone, and CFS with depression groups, respectively). There was a significant effect of flanker condition on information processing speed, $F(2, 134) = 254.39$, $p < .05$. Information processing speed was slowest in the incongruent flanker condition and fastest in the neutral flanker condition for all groups ($p < .05$; Figure 2b). However, healthy controls responded to increases in task complexity in a relatively linear fashion compared to both CFS groups – slower as complexity increased (neutral < congruent < incongruent, $p < .05$). In contrast, both CFS groups responded at a similar, fairly flat rate across groups in response to the neutral and congruent conditions ($p > .05$), and performance in both groups rapidly deteriorated in response to the incongruent, most complex condition (neutral, congruent < incongruent, $p < .05$; Figure 2b). Significant effect of group in RT was observed, $F(2, 67) = 3.78, p < .05$; *post-hoc* analysis revealed that CFS patients with depression took significantly ($p < .05$) longer than healthy controls to process information for all flanker conditions (Figure 2b). Patients with CFS alone had significantly ($p < .05$) longer RTs than healthy controls, but only for the incongruent flanker condition (Figure 2b). There was a tendency for a group effect on the executive condition, $F(2, 67) = 2.92$, $p < .10$. *Post-hoc* analysis revealed that both patient groups (CFS alone: 161 ± 63 ms; CFS with depression: 161 ± 105 ms) had a tendency ($p < .10$) to have longer latencies in the conflict condition requiring executive control than healthy controls (118 ± 47 ms).

Discussion

We evaluated CFS patients on the ANT task to test whether their information processing was impaired. We found no differences among groups of CFS patients with comorbid major depressive disorder, CFS patients without comorbid major depressive disorder, and controls in error rates in the performance of the ANT. In contrast, information processing speed to perform these tasks clearly differentiated patients from controls – most strikingly in the incongruent condition (Figure 2), which requires the most efficient information processing. Both patient groups had longer latencies in the conflict condition requiring executive control, but not in the alerting or orienting conditions. Thus, the findings of this study confirm our hypothesis and support a previous finding (Deluca *et al.*, 2004), showing that cognitive difficulties reported by CFS patients are due to slowed information processing. As previously reported (Deluca *et al.*, 2004) and confirmed here, response accuracy is not a reliable outcome measure of cognitive dysfunction in CFS. Instead information processing speed – as reflected by increased RT – is the desired endpoint to evaluate subtle information processing deficits in CFS. In addition, our findings underscore the necessity to use neuropsychological tasks that require complex information processing to elicit and document problems in information processing in CFS. Usually complex neuropsychological measures that challenge the executive control network are used to achieve this goal (Deluca *et al.*, 1997, 2004). The executive control network is thought to be active when we face situations that require self-regulation of cognitions and emotions, such as planning, making a decision, detecting errors, giving a novel response, or overcoming habitual actions (Norman & Shallice, 1986). It is most frequently measured by requiring a response to one feature of a stimulus while ignoring another dominant feature of a stimulus. We established here that the ANT is a task that fulfils these requirements and can be easily used by clinicians to screen for information processing difficulties in their CFS patients.

It can be hypothesized that the reduced ability to detect, identify, and react to a conflict situation (congruency of flankers) is a consequence of poor information processing speed. Although some studies indicate that cognitive deficits in CFS are not related to working memory deficits (Deluca *et al.*, 2004), it is plausible that slow information processing speed also affects working memory capacity as encoding of pertinent information is slower, not enough necessary information may be stored to perform efficient information processing. Specifically, CFS patients commonly complain about difficulties with quick decision-making under challenging conditions not unlike those similar to the flanker task. When queried about what type of difficulties they encountered, they often answer that they have difficulties to easily call up the instructions without having to refresh them in memory.

Chronic fatigue syndrome patients are frequently depressed. Depression increases simple RT, and antidepressant treatment shortens it (Kalb, Dorner, & Kalb, 2006). In this study, participants with CFS and depression had the longest RTs in both simple RT and the ANT despite their being on treatment. Simple RT reflects the time it takes to detect a stimulus and execute a motor response to it (Jaskowski, 1996). By subtracting simple RT from RT obtained with the flanker task, we could control for the time taken to mentally process the central stimulus and flankers (i.e., information processing speed). The fact that the information processing speed of the CFS group with depression was not significantly different from that in the CFS alone group (Figure 2a and b), however, indicates that depression *per se* is not responsible for CFS patients' problems with information processing, although depression may add to the overall cognitive impairment.

We also note that one potential confounder, namely lack of effort, does not appear to explain the current results. Lack of effort would manifest itself in decreases in RT combined with increases in error rates over time. CFS patients showed neither of these effects over three blocks in the flanker task, RT for CFS alone: first block, 699 ± 148 ms; second block, 678 ± 178 ms; third block, 700 ± 199 ms; $F(2, 36) = 1.26, p > .05$, error rate for CFS alone: first block, 0.60 ± 1.06%; second block, 0.82 ± 1.37%; third block, 1.10 ± 1.79%; $F(2, 36) = 1.04$, $p > .05$. Because these motivational factors cannot explain the results, slowed information processing speed in CFS patients might indicate that they have to work harder than healthy individuals to complete the same task. In a prior neuroimaging study, Lange *et al.* (2005) also found evidence for this idea. They found that CFS patients were able to process auditory information as accurately as healthy controls but utilized more extensive regions of the network associated with the verbal working memory, suggesting the possibility of CNS dysfunction in those with CFS. Thus, although patients perceive they have significant problems in completing cognitive tasks, this may relate to their perception that they need to exert more mental effort to complete a task accurately if time is limited. This increased mental demand may result in increased error rates for CFS patients under some circumstances, particularly when the task demands are high or prolonged and the task is time limited. Our results suggest that the ANT may be a simple and objective test for revealing the specific cognitive deficits associated with CFS. We are currently collecting normative data and will evaluate whether the computerized information processing task utilized in this study can be used effectively in clinical practice. A recent psychometric examination of the ANT reveals that the executive function scores have the highest reliability of the three attentional functions reflected in the ANT, suggesting the possibility that subtle differences in alerting or orienting functions could exist, but that this study may not have sufficient power to overcome the lower reliabilities of the alerting and orienting components (Macleod *et al.*, 2010). An important limitation should also be noted. First, many if not most individuals with CFS, either with or without depression, were medicated. Thus, medication effects could account in part for the findings here. However, the fact that both CFS groups were taking similar medications suggests that potential medication effects primarily limit the interpretation of comparisons of the two CFS groups with the healthy controls, and should have less affect on comparisons between the two CFS groups.

In conclusion, our results show that cognitive difficulties reported by CFS patients might be due to slowed information processing accentuated on tasks that require executive functioning. This underscores the necessity to use neuropsychological tasks that require tasks of cognitive conflict to elicit and document problems in information processing in CFS. As the ANT can be easily administered via computer, it may be a task that could be used clinically to assess information processing deficits in individuals with CFS.

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