Parkinsonism and Related Disorders 21 (2015) 1306–1311

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Selective attentional deficit in essential tremor: Evidence from the attention network test

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ARTICLE INFO

Article history:
Received 30 April 2015
Received in revised form
8 August 2015
Accepted 30 August 2015

Keywords:
Attention
Essential tremor
ANT
Reaction time
Alerting

ABSTRACT

Introduction: The traditional view of essential tremor (ET) as a monosymptomatic and benign disorder has been reconsidered after patients with ET have been shown to experience cognitive deficits that are also related to attention. The Attention Network Test (ANT) is a rapid, widely used test to measure the efficiency of three attentional networks, i.e. alerting, orienting and executive, by evaluating reaction times (RTs) in response to visual stimuli. The aim of this study was to investigate attentional functioning in ET patients by means of the ANT.

Methods: 21 non-demented patients with ET and 21 age- and sex-matched healthy controls performed the ANT.

Results: RT was significantly longer in ET patients than in controls ($p < 0.001$). Moreover, a significant difference in alerting and executive efficiency ($p = 0.003$ and $p = 0.01$ respectively) was found between groups, while the difference in the orienting efficiency only bordered on significance.

Conclusion: Our results point to a difficulty in the alerting and executive domains of attention in ET patients, probably owing to a dysfunction in the cerebello-thalamo-cortical loop. These selective attentional deficits are not related to clinical motor symptoms, contributing to shed further light on the clinical picture of ET.

1. Introduction

Essential Tremor (ET), which is clinically characterized by an 8- to 12-Hz kinetic tremor of the arms and is often accompanied by head and voice tremors, represents the most common tremor disorder in humans [1]. Similarly to others movement disorders, the traditional view of ET as a monosymptomatic and benign disorder has now been reconsidered after patients with ET have been shown to experience cognitive deficits, which are typically mild but progressive [2].

The cognitive features of ET, which have been investigated by means of neuropsychological tests and neuroimaging and electrophysiological tools, are mainly related to the executive functions [3–6], though attentional deficits have also been implicated. In particular, subgroups of ET patients have displayed deficits in complex auditory attention and visual attention, as well as some peculiar attentional deficits measured by eliciting psychophysiological components, such as P3 and MMN, that are related to the evaluation of novelty and pre-attentive auditory discrimination [7,8].

Attention is a major cognitive function that may be defined in terms of the ability to correctly allocate processing resources to relevant stimuli [9]. It does not consist of a single mechanism, but

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http://dx.doi.org/10.1016/j.parkreldis.2015.08.035
1353-8020/

rather of a complex system that oversees distinct neuronal circuits [10].

One early influential model, based on the hypothesis that attention has various neurological underpinnings, was first proposed by Michael Posner: the Attention Network Theory stated that there are at least three key types of supramodal attention, i.e. alerting, orienting and executive, each of which is functionally and anatomically distinct [11].

The alerting network is designed to achieve and maintain an internal state in preparation for perceiving the incoming stimuli. Neuroimaging studies have demonstrated that this network is related to an increased activity in the thalamus and in the fronto-parietal cortical networks, especially in the right hemisphere, and it has been associated to the norepinephrine system arising in the locus coeruleus. The orienting network is aimed at prioritizing sensory input by selecting information and shifting the attentional focus from one area or object to another in the visual field. It has been related to the superior parietal lobe, the temporal parietal junction, the frontal eye fields, and the pulvinar, and it has been associated to the acetylcholine system. The executive network serves to monitor and solve conflicts between competing information computed in different neural areas. It is linked to the activity of the anterior cingular cortex (ACC) and the lateral prefrontal cortex, and its functioning is influenced by the dopamine system [10–13].

Although these three networks are related to specific anatomies and neurotransmitters and have a certain degree of independence, interactions may occur [14]. An easy and reliable way to study these three attentional networks is by means of the Attentional Network Test (ANT), which was first proposed by Fan [14] and which, by combining the cued reaction time task and the flanker task, yields a measure of the efficiency of these three networks within one relatively short task that can be easily run with patients, even affected by movement disorders.

Even if there is a growing body of evidence regarding the cognitive impairment in ET patients, the pathophysiology of cognitive deficits in ET, as well as of ET itself, is still poorly understood. Many authors have attributed these deficits to a frontal dysfunction caused by a remote effect within cerebello-thalamo-cortical circuits due to the primary cerebellar pathology [15], supported by functional imaging showing abnormal activities in dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex of ET patients performing cognitive task [16,17] and by structural imaging showing widespread areas of atrophy in both cerebellar and cerebral areas, especially frontal lobe-ACC and prefrontal cortices [18].

The aim of the present study was to verify, by means of the ANT, whether a selective attentional deficit, according to the Posnerian model, is present in ET patients in order to better define the cognitive pattern of ET from a neural networks' efficiency perspective. We hypothesized, given the body of evidence collected over the last decade on cognitive deficits in ET, which mainly highlighted the role of cerebellum and cortical areas implicated in executive functions, that patients experience difficulties related to the executive network. We also tried to assess the efficiency of the orienting and alerting domains that so far have not been well investigated.

2. Subjects and methods

2.1. Subjects

Twenty-one outpatients (10 males, 11 females; 72.4 ± 7 years), with a diagnosis of ET [19], were consecutively recruited for the study at our clinic between July 2014 and December 2014.

All the patients were examined by two independent experienced neurologists and were clinically evaluated by means of the Fahn–Tolosa–Marin Tremor Rating Scale (FTM–TRS) [20].

The main clinical characteristics of the ET population are shown in Table 1. At the time of the study, 6 (28.6%) patients were taking betablockers, 4 (19%) were taking levetiracetam, while the remaining 11 (52.4%) were not taking any medication.

Twenty-one healthy age- and sex-matched volunteers (10 males, 11 females; 71.8 ± 7.7 years), with unremarkable personal and family histories for psychiatric and neurological disorders and no abnormalities at the neurological examination, were consecutively recruited from non-consanguineous relatives of the neurological outpatients as the control group in the same period. None of the controls was taking any medication.

All the subjects enrolled in the study underwent the Mini-Mental State Examination to rule out the presence of dementia. All the participants were right-handed and gave their written informed consent to the study. The study was approved by the local ethics committee.

2.2. Procedure

2.2.1. Control measures

Before the ANT session, validated self-administered questionnaires were used to assess depression (Beck Depression Inventory, BDI) [21] and anxiety (STAI Y-1, STAI Y-2) [22] in order to rule out the presence of attentional biases determined by anxiety and depression symptoms.

2.2.2. Paradigm: attention network test

The ANT we used is the original version of the test, described by Fan et al. [14].

The task requires participants to determine whether a central arrow points left or right, responding as quickly and accurately as possible by pressing one button for the left-pointing arrow and another button for the right-pointing arrow. The arrow appears above or below the fixation point (a central cross shown on a computer screen); it may or may be not preceded by a warning cue (represented by an asterisk), and may or may be not accompanied by flankers (two arrows on either side). There are four cue conditions: (1) "no cue", in which no asterisk precedes the target; (2) "double cue", in which the asterisk appears simultaneously both above and below the center; (3) "center cue", in which the asterisk appears in the center of the screen and indicates that the target arrow is about to appear, without providing any information on its location; (4) "spatial cue", in which the asterisk appears either above or below the center, indicating that the arrow is about to appear and exactly where it will appear. There are also three target conditions according to the presence and type of flankers: (1) "neutral" condition, in which the target is not surrounded by flankers; (2) "congruent" condition, in which the four arrows surrounding the central target point in the same direction; (3) "incongruent" condition, in which they point in the opposite direction.

Measuring how RT are influenced by alerting cues (no cue versus double cue), spatial cues (center cue versus spatial cue), and flankers (congruent versus incongruent) provides a measure of the efficiency of the three attentional networks: when the double cue is presented it tends to keep attention towards to two potential target locations (below or above the fixation point), but it also provides temporal information alerting the subject to the impending arrival of the target stimulus, so that recruiting the alerting network. Both center and spatial cues are alerting cues, but only the spatial cue provides spatial information that allows subjects to start orienting attention to the appropriate location while attending the target,