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BRIEF COMMUNICATION

Cognitive functioning in individuals with "benign" essential tremor

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Abstract

Essential tremor (ET) is the most common type of movement disorder, although its etiology and neurophysiological substrates remain unclear. While thought to be a benign condition, it has yet to be studied from a neuropsychological perspective. We examined the neurocognitive functioning of 13 nondemented subjects with severe ET, including aspects of memory, cognitive flexibility, and attention. Results revealed that 12/13 subjects demonstrated impairment on 1 or more cognitive measures in comparison with published normative data. The pattern of findings was suggestive of relative dysfunction of frontal-mediated processes not unlike that seen in Parkinson's disease. These deficits were found in subjects irrespective of the presence of cognitive complaints, depression, or the existence of other potential neurocognitive risk factors. These findings suggest that mild cognitive deficits are not uncommon in association with severe ET and may be related to subcortical systems. (*JINS*, 2002, *8*, 125–129.)

Keywords: Essential tremor, Cognitive functioning, Movement disorders, Neuropsychology

INTRODUCTION

Essential tremor (ET) is the most common type of movement disorder, affecting more than 5,000,000 individuals over the age of 40 in the United States (Hubble et al., 1989). The disorder is characterized by postural and action tremors predominantly occurring in the upper extremities, and is inherited as an autosomal dominant trait in at least 50% of cases. Currently, no biochemical or pathological abnormalities have been identified, and despite promising studies in the field of neurophysiology implicating structures in the basal ganglia, the etiology remains unclear (Hua et al., 1998). Speculation of cerebellar involvement in ET has also been gaining support, as positron emission tomography and functional magnetic resonance imaging studies have found increased activation of the cerebellum (among other brain regions) in patients with ET when asked to extend their arm(s) (Bucher et al., 1997).

Since essential tremor is not thought to be associated with other neurological deficits and does not appear to affect life expectancy, the prefix "benign" is frequently used to describe the disorder. However, the use of the term benign may be misleading, as patients with ET endorse greater social, communication, emotional, and physical difficulties than controls, in addition to disruption of work, home, and recreational activities (Busenbark et al., 1991). To date, neuropsychological function in patients with ET has received little, if any, attention, and we know of no published investigations of cognitive status in this population. Given the importance of basal ganglia structures and associated frontosubcortical circuits in various aspects of cognitive functioning, it was hypothesized that subclinical or mild neurobehavioral deficits may exist in some individuals with ET. The present study is a preliminary exploratory effort to examine the neurocognitive functioning in a sample of individuals with severe ET who were otherwise healthy at the time of evaluation.

METHODS

Subjects included 13 individuals with bilateral tremor who met diagnostic criteria for classic ET (Deuschl et al., 1998), which consists of the presence of bilateral, largely symmetric postural or kinetic tremor involving the hands and fore-

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arms when the limbs are outstretched that is visible and persistent. All patients were diagnosed by a neurologist specializing in movement disorders who carefully excluded patients with other possible causes of tremor such as Parkinson's disease or other Parkinson plus syndromes. Subjects were seen for neuropsychological assessment as part of a comprehensive evaluation for potential surgical treatment of their tremor. Thus, subjects' tremors were both severe and intractable to medical management. Four of the 13 patients were taking medication to help control their tremors (Neurontin = 1, Inderal = 1, Mysoline = 1, Inderal + Mysoline = 1), but reported minimal if any benefit from their medication. Cranial MRI results were available for 12/13 patients and were notable for mild microvascular ischemic changes associated with normal aging in many of the patients, but not significant enough to account for their tremors. One patient had several old infarcts in the basal ganglia and internal capsule, but these were not thought to be causally related to the tremor and there was no clinical evidence or cognitive changes suggestive of a stroke.

The ET sample consisted of 8 males and 5 females (9 right-handed, 4 left-handed), with a mean age of 70.8 years (SD = 11.8, range = 43–86) and a mean education level of 11.6 years (SD = 3.8, range = 7–18). Intellectual functioning of the group as a whole was average, with a mean estimated Full Scale IQ of 96.5 (SD = 13.9, range = 80–120). All subjects obtained a score of 25 or higher (M = 27.5, SD = 1.5, range = 25–30) on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). Mild cognitive complaints (e.g., forgetfulness, word-finding difficulties) were reported in 54% of subjects, but were not thought to significantly impact their daily functioning (according to the patients), and none met criteria for dementia. Possible concomitant neurocognitive risk factors included: hypertension (n = 5), diabetes (n = 1), prior breast cancer and treatment (n = 2), seizure disorder (n = 1), hypothyroidism (n = 1), and past or current depression (n = 3). However, each of these conditions was reportedly well-controlled, and none of the subjects acknowledged any know neurological insults (e.g., stroke, head injury). Family history of dementia or memory impairment was reported in only 1 case.

A group of 13 nondemented subjects diagnosed with Parkinson's disease (PD; 7 females, 6 males, all right-handed) was included for neuropsychological profile comparison, since PD is probably the most common movement disorder after ET. Subjects were diagnosed by the same neurologist and had to manifest at least two of three cardinal signs of PD (resting tremor, bradykinesia, rigidity) and demonstrate an unequivocal response to levodopa. All had advanced disease and were surgical candidates for treatment of their motor symptoms. PD subjects were selected to be similar in age and education to the ET group. While they were slightly younger (M = 66.2 years, SD = 4.6) and better educated (M = 13.2 years, SD = 2.0) than ET subjects, there were no significant differences between the groups for age [$t(24)$ = 1.3, p = .20], or education [$t(24)$ = −1.5, p = .16]. Full Scale IQ (M = 96.7, SD = 8.4) and MMSE (M = 27.9, SD = 1.0) scores also did not differ between groups [$t(23)$ = −.82, p = .42; $t(21)$ = −.04, p = .97, respectively].

The following measures were selected from a larger battery of tests for examination in this study to provide a sampling of the major cognitive domains: California Verbal Learning Test (CVLT; Delis et al., 1987), Wechsler Memory Scale–Revised Visual Reproduction (WMS–R VR; Wechsler, 1987), Wisconsin Card Sorting Test (WCST; Heaton et al., 1993), Boston Naming Test (BNT; Kaplan et al., 1983), letter (FAS) and animal fluency (Spreen & Strauss, 1998), WAIS–R Block Design subtest (age scaled score; WAIS–R BD; Wechsler, 1981), Ruff Figural Fluency Test (Ruff, 1988), Victoria Stroop (last trial time in seconds; Regard, 1981), and Beck Depression Inventory (BDI; Beck et al., 1979). Subjects' scores were analyzed in comparison with normative data found in test administration manuals or other published references (Heaton et al., 1991; Spreen & Strauss, 1991, 1998), all of which corrected for age and many of which corrected for age and education.

RESULTS

Table 1 presents the means, standard deviations, and ranges of scores for the ET sample on the selected neurocognitive variables, as well as the percentage of subjects who scored more than one standard deviation below the mean of the normative sample for each measure. Analysis of test scores for each individual revealed that 50% or more of subjects demonstrated evidence of at least mild impairment (defined as performing 1 or more SD below the normative mean) on at least 5/10 measures (see Table 1). Of note, the patient with old basal ganglia and internal capsule infarcts performed in the impaired range on only 1 of the 10 measures. PD and ET subjects' scores for each measure were converted to T scores for presentation in Figure 1. As can be seen in the figure, the ET group as a whole performed at least one standard deviation below the mean on measures of cognitive flexibility (WCST categories), figural fluency (Ruff designs), and selective attention (Victoria Stroop). In addition, the ET sample approached one standard deviation below average on measures of nonverbal memory (WMS–R VR percent retention), letter fluency (FAS), and aspects of problem solving (WCST perseverative responses). Alternatively, verbal memory (CVLT), confrontation naming (BNT), animal fluency, and constructional abilities (WAIS–R Block Design) were generally within normal limits for the ET group as whole. A similar pattern was seen in the PD group, although these subjects had slightly greater difficulty in comparison with the ET group in the areas of verbal learning, animal fluency, and WAIS–R Block Design performance. In contrast, they performed slightly better on the WCST, Ruff Figural Fluency Test, and the Stroop.

Three of the 13 ET patients endorsed mild depressive symptomatology on the BDI (scores = 12–14) and 1 subject endorsed a moderate degree of symptoms, with a score of 20. Neuropsychological patterns of performance were examined for subjects with BDI scores of less than 10 and

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Table 1. Means, standard deviations, ranges, and percent impaired across neuropsychological variables for subjects with essential tremor

Variable	*M*	*SD*	Range	% ≥ 1 *SD* below *M*	% ≥ 2 *SD* below *M*
CVLT Total Raw Score	41.9	12.0	22–61	46	8
WMS–R VR % Retention	55.9	31.3	0–94	31	15
WCST Persev Responses	45.4	27.4	7–115	54	8
WCST Categories	1.9	1.8	0–6	85	69
Boston Naming Test	50.5	6.4	35–58	8	0
Letter Fluency (FAS)	26.0	9.7	11–48	46	8
Animal Fluency	15.4	4.0	10–24	23	8
WAIS–R Block Design (age SS)	9.3	2.6	6–13	15	0
Ruff Total Designs	42.5	17.3	25–90	85	15
Victoria Stroop	55.0	23.0	27–99	58	17

Note. CVLT = California Verbal Learning Test; WMS–R VR = Wechsler Memory Scale–Revised Visual Reproduction; WCST = Wisconsin Card Sorting Test.

more than 10. Aside from greater difficulty on the Stroop and overall learning on the CVLT in patients with a BDI score of greater than 10, overall profiles were similar across subjects. The PD group showed higher scores on the BDI ($M = 13.6$, $SD = 8.6$) than those with ET ($M = 8.2$, $SD = 5.2$), although this difference was not significant [$t(24) = -1.9$, $p = .07$].

DISCUSSION

Despite the lack of cognitive complaints in many ET subjects, 12/13 demonstrated at least mild impairment on one or more cognitive measures, and one-half of the sample showed deficits on 50% or more of the measures, including those without any known neurocognitive risk factors. Examination of the pattern of deficits across the ET group revealed that subjects tended to have the most difficulty on tasks associated with initiation, executive function and memory, while performing within expectation on most language measures. Similar patterns were seen in the PD group and have been reported in individuals with other subcortical movement disorders (e.g., progressive supranuclear palsy), in which basic language and learning abilities are often relatively preserved, while the ability to generate problem-solving strategies and spontaneously use stored information is impaired (Cummings & Benson, 1984). Qualitative analysis of subjects' performance within certain tests may provide further support from a neuropsychological standpoint of possible subcortical dysfunction in individuals with ET. As an illustration, 23% of ET subjects obtained significantly better (≥1 *SD*) scores on delayed recognition testing than free recall on the CVLT, which is a common subcortical finding on this measure (Delis et al., 1991), and one found in 46% of our PD sample. Therefore, the proposed mechanisms that underlie ET (i.e., basal ganglia dysfunction) may also contribute to cognitive inefficiency via disruption of frontostriatal systems, as reported in other basal ganglia disorders.

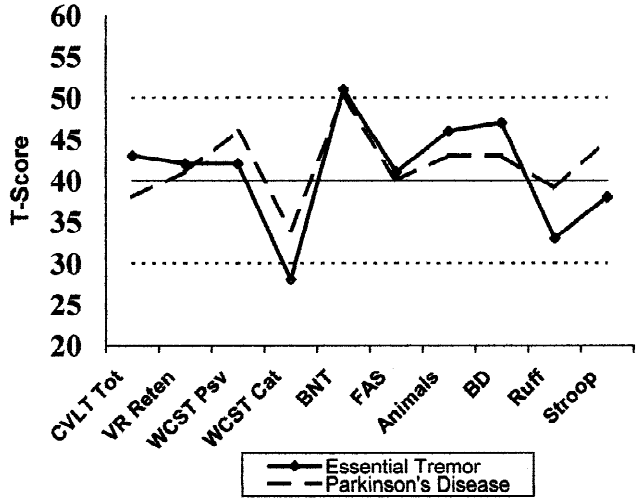

Fig. 1. Mean *T* Scores across neuropsychological variables. VR Reten = Wechsler Memory Scale–Revised Visual Reproduction percent retention, WCST Psv = Wisconsin Card Sorting Test perseverative responses, WCST Cat = Wisconsin Card Sorting Test Categories completed, BNT = Boston Naming Test, BD = Wechsler Adult Intelligence Scale–Revised Block Design age scaled score, Stroop = (Victoria version, last trial–time in seconds).

Similar neuropsychological patterns have been associated with disruption to frontosubcortical systems produced by isolated lesions in specific cortical (frontal lobes) and/or subcortical regions (e.g., thalamus; Van der Werf et al., 2000). Disruption of one of the frontosubcortical circuits that involves communication from and to the cortex and the thalamus via the striatum and globus pallidus and indirectly through the subthalamic nucleus (Tröster, 1998) can also produce such deficits. The current results may provide support for involvement of other brain regions in the development of ET, as some of the group's relative cognitive deficits (e.g., executive functioning, verbal fluency) were similar to those that have been reported in individuals with specific

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cerebellar disorders (e.g., stroke, focal cerebellum atrophy; Daum & Ackermann, 1997), and connections between the cerebellum and other cortical regions (e.g., via frontal pathways) are becoming more widely understood and accepted. Likewise, numerous case reports have been described that demonstrate the role of the thalamus in memory, executive function, and aspects of language (Van der Werf et al., 2000), and the potential involvement of the thalamus in essential tremor is unknown.

While some ET subjects possessed various neurocognitive risk factors that could have contributed to the cognitive deficits identified, the similar pattern of impairments across subjects and in comparison to a group of subjects with Parkinson's disease suggests a more uniform process. However, the presence of other neurological conditions and depression in some patients may have accentuated cognitive impairment associated with ET. In addition, subjects' motor difficulties may have also contributed to their reduced performances on some tasks and likely explains why the ET group performed more poorly than the PD group on figural fluency. However, patients' tremors were not thought to significantly impact most of the individual test scores, and many of the tasks do not involve a timed motor component. Furthermore, some leniency was given in scoring drawings from the WMS–R VR due to the potential impact of tremor. Figure 1 indicates that the ET group scored slightly below PD subjects on WCST categories, Ruff and Stroop. Only the figural fluency test has a primary motor component, and in conjunction with the similarity of the profiles, the ET group's difficulties on the WCST and Stroop are all the more intriguing from a subcortical dysfunction standpoint. Nonetheless, it should be noted that subjects in both patient groups had advanced movement disorders, which may limit the generalizability of these results to those with less severe conditions.

Given the small sample size, it was not possible to thoroughly examine the various factors which distinguish those with ET who develop cognitive problems from those who do not. For example, the 4 ET subjects who were taking medication to treat their tremors each demonstrated impairment on 50% of more of the tests examined, but it is unclear if their tremors were more severe than the other subjects, or if other factors such as disease duration may have contributed, as quantifiable information along these lines was unavailable. The presence of depressive symptomatology may have contributed to increased difficulty with attention in some subjects, but did not appear to differentially affect other cognitive domains in this study when the neuropsychological profiles of subjects with higher and lower scores on the BDI were compared. Further research is clearly needed to confirm these findings and clarify what if any factors may differentiate groups of impaired *versus* nonimpaired patients with ET, including additional examination of duration of illness, severity of tremor, presence of other medical problems, affective disturbance, and effects of medication.

These findings suggest the need for further exploration of possible neuropsychological concomitants of ET in a larger and more demographically balanced (e.g., age, gender) sample. The inclusion of additional comparison populations, including healthy controls and more carefully matched patient groups, may also help to shed more light on the significance of the cognitive abnormalities identified in this sample. Nevertheless, despite the small sample size and heterogeneity of the subjects in terms of age and presence of possible cognitive risk factors, our data provide preliminary evidence of an association between mild cognitive deficits and severe "benign" essential tremor, which we postulate is related to underlying subcortical systems.

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