ESSENTIAL TREMOR: PARADOXICAL VISUOSPATIAL COGNITION

By

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To the volunteers of this study

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Essential tremor (ET) is the most common tremor disorder in humans and is associated with older age. In this condition, tremor manifests from pathological processes involving the cerebellum and primarily occurs during intentional movement of the hands and arms. When severe, it can lead to dysfunction, even impairment, in activities of daily living. ET is also associated with non-motor symptoms, and a handful of studies addressing cognitive functioning in ET have emerged within the past decade. While these studies have consistently described mild deficits in fronto-executive functions (i.e., attention, verbal fluency, set-shifting), visuospatial functioning has been described much more variably.

The present study is the first to focus on visuospatial functioning in ET with a hypothesis-driven, experimental approach. Based on a preliminary neuropsychological study and other structural neuroimaging data, it was hypothesized that visuospatial functioning in ET is related to a counterintuitive clinical phenomenon, i.e., that greater tremor severity in ET is predictive of *better* spatial cognition. Although progressive neurological conditions are generally associated with cognitive decline, it is feasible that patients with more severe intention tremor of the hands tend to develop better spatial

abilities via various compensatory mechanisms, e.g., greater attention needed for continuously judging and monitoring spatial aspects of the environment (particularly distances between the hands and nearby objects for use or avoidance).

This hypothesis was tested in the present study with cognitive / behavioral measures. Individuals with ET were recruited and categorized into a severe or mild tremor group, then tested comprehensively along with controls on various clinical and experimental measures of visual cognition (spatial tests and object/form tests). Results showed that the severe ET group indeed outperformed the mild ET group on two measures of spatial ability, a mental rotation measure and a spatial memory/navigation measure. The two groups were comparable in demographic and mood variables, and the mild ET group demonstrated better fronto-executive scores than the severe group. Neither patient group performed better than normal controls on any measure. Regression analyses showed that tremor severity in ET positively predicted better mental rotation ability and spatial memory, above and beyond other demographic, cognitive, and mood predictor variables. These findings support the notion that compensation for tremor in ET is associated with improvement spatial skills, particularly on tasks with action-based, dynamic components.

CHAPTER 1
OVERVIEW AND AIMS

Essential tremor (ET) is the most common age-associated neurological tremor disorder in the United States. In this condition, tremor (predominantly in the hands and arms) manifests during purposeful movements and can impair daily activities when severe. Disturbances in cognitive functioning also have been described in the emerging literature, particularly mild deficits in fronto-executive functioning (e.g., set shifting, speeded fluency). Visuospatial functioning, the focus of the present study, has been described much more variably. Some studies have demonstrated relatively intact performance on visuospatial tests, while others have described mild impairments. Other evidence suggests that visuospatial functioning in ET may be unusually high.

The basis for these divergent visuospatial findings is unclear. One possibility is that of methodological variance across studies. Usually, only one or two tests have been used to study visuospatial functioning in small, ill-characterized samples, often with no specific hypotheses or predictions. Moreover, a wide variety of tests have been used to study visuospatial functioning, so the divergent findings in this literature may be a function of the type of test used. Some studies lack appropriate attention to screening methods for general cognitive impairment, and many others have used visuo-constructional tests that require efficient fine-motor manipulations of objects (e.g., a pencil or small blocks), potentially problematic for patients with a tremor disorder. For these reasons, prior studies likely have underestimated visuospatial functioning in ET.

Beyond poor methodological control, the divergent characterizations of visuospatial functioning in ET might be related to some systematic, clinical phenomenon, such as markers of disease severity (e.g., severity of tremor). While one might expect that greater disease severity would be predictive of poorer visuospatial ability, a preliminary study found surprisingly high spatial abilities among the majority of a group of relatively older and severely impaired pre-surgical ET patients (19 of 22) (Springer, Chang, Graf-Radford, Jacobson, Crucian, Okun et al., 2006). A separate study of another ET sample and controls yielded structural neuroimaging data that complement these behavioral findings. Specifically, areas of the brain used in spatial processing were found to be relatively dense in ET patients with more severe and longstanding intention tremor of the arms; however, ET patients with little or no upper extremity action tremor showed typical age-related decline in these visuospatial areas of the cortex (Daniels, Peller, Wolff, Alfke, Witt, Gaser et al., 2006). Taken together, these findings are suggestive of a paradoxical phenomenon: more severe disease (i.e., upper extremity intention tremor) may be related to better visuospatial functioning in ET. The behavioral data and structural neuroimaging data of these previous studies also suggest that this relationship (if legitimate) may hold only for judgments about spatial relationships, but not other aspects of visual cognition.

This proposed relationship is counterintuitive and necessitates the suggestion of an explanatory mechanism. Feasibly, patients with more severe upper extremity tremor need to recruit greater compensatory skills to maintain similar functional levels. These skills likely involve visuospatial functions (e.g., spatial judgments, visuomotor tracking), because patients with intention tremor are affected primarily while reaching for, manipulating, or avoiding nearby objects. Over time, patients likely undergo “practice” of these skills, leading to measurable improvements on cognitive tasks and neuroplastic changes in spatial areas of the brain.

The overall aims of this study were twofold. The first aim was designed to test the hypothesis that relatively severe upper arm tremor in ET is associated with better visuospatial skills relative to ET patients with milder arm tremor. This hypothesized relationship was constrained to spatial tasks only, and not those requiring judgments regarding feature recognition/discrimination (paralleling the theoretical distinction between spatial and object/form visual streams of information processing by Ungerleider and Mishkin, 1982). The second aim of this study was designed to address and rule out other variables contributing to visuospatial functioning, should a counterintuitively positive relationship between disease severity and visuospatial functioning be demonstrated in the preliminary analyses. More specifically, the contribution of disease severity to spatial abilities in ET was tested, above and beyond other sociodemographic, cognitive, and mood predictor variables. To meet these aims, various clinical and experimental tasks requiring different types of spatial and object/form processing were administered to individuals with varying degrees of tremor severity, as well as to normal controls. Neither of the ET groups was expected to outperform the controls on either the spatial tasks or the object/form tasks.

The following chapter provides a detailed theoretical backdrop for this study, including sufficient background for ET as a disorder, a discussion of behavioral and structural plasticity in neurological disease and older age, and a discussion of subtypes of visuospatial processing. The specific aims and hypotheses are detailed in the subsequent chapter (Chapter 3).

CHAPTER 2
BACKGROUND AND SIGNIFICANCE

Essential Tremor (ET)

The central topic of this dissertation is visuospatial functioning in essential tremor (ET). This chapter provides background information relevant to this topic and highlights the importance of this line of research. Prior to a discussion of visuospatial functioning in ET, however, it is necessary to provide an overview of the disorder itself. Therefore, this initial section of this chapter briefly covers the presentation, impact, neuropathology, and treatment of ET.

ET is recognized as the most common neurological tremor disorder in humans (Rautakorpi, Takala, Marttila, Sievers, & Rinne, 1982; Benito-Leon & Louis, 2006). It has been estimated as 20 times more common than Parkinson's disease and has a prevalence of about 4.0% in the general population (Dogu, Sevim, Camdeviren, Sasmaz, Bugdayci, Aral, et al., 2003). In people over 65 years of age, the prevalence rate is higher, with estimates ranging between 9% and 14% (Moghal, Rajput, D'Arcy, & Rajput, 1994; Louis, Marder, Cote, Wilder, Tang, Lantigua, et al., 1996).

ET is characterized most commonly by bilateral kinetic/action and postural tremor of the upper extremities, that is, tremor that occurs during voluntary movements or static posing of the arms. While the arms are affected in about 90% of patients, 50% of patients or fewer have tremor in other regions of the body, such as the head (neck) and/or voice (Koller, Busenbark, & Miner, 1994). The trunk or legs are affected more rarely and usually after the onset of arm tremor, suggesting that ET initially affects the arms and then spreads to other regions of the body as the disease progresses (Louis, Ford, & Frucht, 2003). Longitudinal studies and anecdotal reports indicate that the progression of ET tends to be relatively gradual, although the course of the disease can vary considerably across individuals (Elble, 2000; Putzke, Whaley, Baba, Wszolek, & Uitti, 2006).

Among those with severe tremor, quality of life can be substantially impaired. Levels of tremor severity in ET have not been formally defined for widespread clinical use, but relatively severe tremor of the arms, for example, can interfere with basic activities of daily living (ADLs), e.g., handling a spoon or glass, buttoning a shirt, or using soap or a toothbrush (Lewis, 2002). Unfortunately, disability does not affect a minority of individuals with ET. Almost three out of four ET patients report some type of disability due to tremor, and many are forced to quit their profession due to disabling shaking (Louis, Barnes, Albert, Cote, Schneier, Pullman et al., 2001).

Converging data from imaging, lesions, and neuropathology studies suggest that the characteristic action tremor of ET is the result of pathological processes localized in the cerebellum or its inflow (ponto-cerebellar) or outflow (cerebello-thalamic-cortical) pathways (Louis, 2006). Indeed, the tremor observed in ET is very similar to that seen after damage to the cerebellum, and cerebellar stroke can completely abolish tremor symptoms altogether (Dupuis, Delwaide, Boucquey, & Gonsette, 1989). Positron emission tomography was used to show that at rest, cerebellar areas are hyperactive by 30-40% in ET patients relative to healthy controls (Wills, Jenkins, Thompson, Findley, & Brooks, 1994). A relatively large, case-controlled, post-mortem study found widespread Purkinje cell loss and a seven-fold increase in cerebellar “torpedoes” (clusters of misaccumulated, disorganized neurofilaments and other organelles) in the majority of ET patients (Louis, Faust, Vonsattel, Honig, Rajput, Robinson, et al., 2007).

First-line medical treatment for easing or negating tremor typically begins with pharmacological agents. The more popularly prescribed and empirically supported agents include beta-adrenergic antagonists (e.g., propranolol) and anticonvulsants (e.g., primidone), although other agents are used as well, including benzodiazepines, botulinum toxin, and atypical antipsychotics (Pahwa, Lyons, & Pahwa, 2005; Zesiewicz, Elble, Louis, Hauser, Sullivan, Dewey, et al., 2005). The majority of patients do not experience major side effects, so medications can substantially improve the quality of life by reducing tremor and associated impairment (Louis, 2006).

Neurosurgical treatment is available for medication-refractory cases. These include thalamotomy or deep brain stimulation surgery of the ventral intermediate nucleus of the thalamus (Lyons & Pahwa, 2004; Okun, Rodriguez, Mikos, Miller, Kellison, Kirsch-Darrow, et al., 2007; Pahwa, Lyons, & Koller, 2000). Both of these procedures are designed to eliminate or lessen tremor by interrupting hyperactive pathways from the cerebellum to fronto-motor pathways via modification of thalamic functioning. Due to the risk of potentially irreversible adverse effects inherent in brain surgery, these procedures are limited to the disabling cases that do not show sufficient response to medications.

Cognitive Functioning in ET

Aside from the primary motor symptoms of ET, mild cognitive changes also have been reported. Neuropsychological studies of ET have emerged in the past decade and have consistently described mild deficits in frontally mediated executive functions such as cognitive inhibition, verbal fluency, and set-shifting (e.g., Benito-Leon, Louis, & Bermejo-Pareja, 2006a; Duane & Vermilion, 2002; Gasparini, Bonifati, Fabrizio, Fabbrini, Brusa, Lenzi et al., 2001; Higginson, Wheelock, Levine, King, Pappas, &

Sigvardt, 2008; Lacritz, Dewey, Giller, & Cullum, 2002; Lombardi, Wollston, Roberts, & Gross, 2001; Sahin, Terzi, Ucak, Yapici, Basoglu, & Onar, 2006; Springer, Chang, Graf-Radford, Jacobson, Crucian, Okun, et al., 2006; Troster, Woods, Fields, Lyons, Pahwa, Higginson et al., 2002). These deficits have been observed in severe, presurgical patients and community dwelling populations and have been attributed to dysregulation of frontal circuits via hyperactive cerebellar-thalamic outflow pathways. Side effects from high levels of tremor-reducing medications (e.g., primidone, propanolol) also have been potentially implicated in these issues; however, relatively young and newly diagnosed “treatment-naïve” ET patients also have been shown to manifest subtle fronto-executive problems, raising doubts as to whether medications are the primary basis for cognitive difficulties in ET (Sahin et al., 2006).

A Preliminary Study: Surprising Visuospatial Findings

At the University of Florida, Springer and colleagues retrospectively examined data from an older and relatively severe group of ET patients (N=24), who was evaluated prior to undergoing DBS surgery through the UF Movement Disorders Center (Springer et al., 2006). The underlying rationale was to determine how the neuropsychological profiles of these severe, older ET patients would differ from those of individuals with Parkinson’s disease. As a first step, the cognitive profile of ET alone was analyzed in an attempt to replicate findings from the literature. It was hypothesized that frontal-executive impairments would also be observed in this severe population, even after eliminating patients from our sample for probable dementia, severe mood disturbances, brain trauma, and little formal education (< 9 years). Neuropsychological measures were used to test several cognitive domains, including memory, language, attention, fronto-executive functioning, and visuospatial functioning. Analyses were designed to examine the proportion of patients experiencing cognitive deficits, with the final sample of pre-surgical patients averaging 70 years of age and 14 years of education.

Consistent with other reports in the literature, the results of these analyses showed that a disproportionate number of ET patients performed poorly on tasks associated with frontal-executive functioning (i.e., measures of inhibition and speeded verbal fluency). Results also indicated, however, that an abnormally large proportion of the sample performed well on the Judgment of Line Orientation (JOLO) task, a clinical visual-spatial task requiring fine discriminations of lines' angular orientations (Benton, Hamsher, Varney, & Spreen, 1983). Specifically, 19 of the 22 ET patients who completed this test scored in the 51st to 100th percentile range relative to age- and gender-corrected norms. As a group, the ET patients scored about half a standard deviation above the 50th percentile. This elevated performance occurred in the context of average memory performance (stories, word list) and another visuoperceptual test of object discrimination (unfamiliar face matching and recognition), in addition to the mild fronto-executive functioning deficits.

The higher-than-expected visuospatial functioning in this severe ET population was a surprising finding. Certainly, previous studies examining visuospatial cognition in ET have shown variability, from descriptions of *deficits* (e.g., Duane & Vermilion, 2006) to "intact" abilities (e.g., Lombardi et al., 2001). However, neurological conditions are not typically associated with relatively better or improved cognitive abilities. In Parkinson's disease, for example, there is evidence to suggest that impairment in visuospatial processing is among one of the most frequently reported cognitive complaints (Growdon & Corkin, 1987). Moreover, the high visuospatial performance in this sample was found the context of mild *deficits* on fronto-executive and other tests. This suggests that the sample showed executive functioning characteristics comparable to other study samples and was not simply gifted across cognitive domains.

Methodological Concerns

The basis for divergent visuospatial findings in the ET literature is unclear and is a central question in this dissertation. There are several possible explanations. One relates to methodological variance. Across cognitive studies in ET, no single test has served as a "common denominator" to assess visuospatial functioning. Because many visuospatial tests are "multifactorial" (in that they are sensitive to variations in factors beyond primary visual processing, especially in tremor disorders), divergent findings across studies might be a product of the type of test or tests used (Waterfall & Crowe, 1986). For example, many tests that are commonly used to measure visuospatial functioning in ET require speeded and complex fine-motor responses, such as copying a detailed line drawing or manipulating small, colored blocks to replicate a target pattern within a certain time limit, e.g., the Rey-Osterrieth Complex Figure Test – Copy Trial (Duane et al., 2002; Kim et al., 2009; Sahin et al., 2006), or the Block Design subtest from the Wechsler Adult Intelligence Scale, Third Edition (Higginson et al., 2008; Lacritz et al., 2002; Sahin et al., 2006; Wechsler, 1997a). Individuals with relatively severe tremor may have a more difficult time on these types of tests, leading to an overall bias toward describing impairments in these studies. Test-specific differences might also occur on non-motor based tasks, simply as a result of differences in test difficulty.

Additionally, not all studies in ET have used adequate screening methods for conditions associated with general cognitive impairment, such as dementia, severe psychiatric impairment, or a history of severe brain trauma. This too may have contributed to an overall bias toward descriptions of visuospatial impairment (as well as impairment in other cognitive domains). Several studies do not report the details of their screening methods, or they failed to mention screening for these conditions altogether (e.g., dementia, as in Lombardi et al., 2001, or Duane & Vermilion, 2001). Because ET has been associated with higher rates of dementia and psychiatric disturbances in some studies (Benito-Leon, Louis, & Bermejo-Pareja, 2006a; Benito-Leon, Louis, & Bermejo-Pareja, 2006b; Schneier, Barnes, Albert, & Louis, 2001), screening for these conditions is especially important for clarifying visuospatial functioning in ET.

“Spatial” vs. “Object/Form” Processing: Subtypes of Visuospatial Cognition

Another consideration for the divergent visuospatial findings in the ET literature relates to theoretical subtypes of visual cognition. It is true that current functional models of the visual brain remain open to debate (Milner & Goodale, 2009), and Carroll (1993) suggested after his comprehensive review of factor-analytic visuospatial studies that the actual number of visuospatial “abilities” may equal the number of different visuospatial tests created. Regardless, a functional model of visual processing may be useful in understanding visuospatial findings in ET studies.

In one highly influential model, Ungerleider and Mishkin (1982) proposed that the raw visual information that reaches the primary visual cortex from the retinal fields bifurcates and is processed further along two separate visual streams, each with separate functions. They posited that the anatomically more ventral processing stream (colloquially dubbed the “what” pathway) projecting to the inferior temporal lobes processes relatively static form features for the purpose of object identification (e.g., facial recognition, or form discrimination). The other processing stream, they suggested, runs dorsally to the parietal lobes (i.e., the “where” pathway) and was theorized to mediate relatively spatial aspects of visual cognition, allowing the perceiver to localize elements of the environment. The forward projections of the two visual streams of processing are relatively segregated before converging in widespread cortical areas, where information is integrated and utilized in higher-order cognition. Areas of convergence include the superior temporal areas and various frontal and prefrontal locations (Goldman-Rakic, 1987; Ungerleider, Courtney, & Haxby, 1998).

In essence, the model of Ungerleider and Mishkin (1982) suggested that the “purpose” of vision is twofold: to recognize and localize elements of the surrounding world. Indeed, this intuitive notion has been supported by several lesion, functional imaging, and electrophysiology studies, which have demonstrated evidence consistent with the idea that the perception of spatial relationships and the perception of objects’ forms indeed occurs via distinct neuroanatomical substrates; i.e., an occipito-parietal stream of visual information processing, and an occipito-temporal route, respectively (Ungerleider & Haxby, 1994). Factor analytic studies also have highlighted a primary distinction between spatial cognition and object/form perception based on performances in brain-injured and healthy populations across a wide variety of visuospatial measures (for review, see Carroll, 1993).

While not free from controversy itself, the theoretical distinction between subtypes of visual processing might help account for the disparate descriptions of visuospatial functioning in ET. In Springer and colleagues’ (2006) study, for example, two visuospatial tests were used, one traditionally considered to measure spatial/dorsal stream functioning (i.e., Benton’s Judgment of Line Orientation), and one traditionally considered to measure object form/ventral stream functioning (i.e., Benton's Facial Recognition Test). The authors found that their severe, pre-surgical ET sample performed as expected on the facial discrimination task but better than expected on the spatial task. The dissociation may be related to differences in functioning between Ungerleider and Mishkin's (1982) two visual streams of processing. It is worthy to note that the pattern observed by Springer et al. (2006) was found in a well-screened, severe ET sample, and with the aid of clinical tests lacking a motor response requirement.

A Hypothesis for Superior Spatial Cognition in ET

The basis of disproportionately high spatial functioning (but not object/form perception) found in severe ET is unclear and seems paradoxical (Springer et al., 2006). A potential explanation might be related to findings from a recent structural neuroimaging study. Daniels and colleagues (2006) used voxel-based morphometry to test the hypothesis that severity of kinetic/action tremor in ET may be associated with cerebellar degeneration. Results failed to confirm this hypothesis, as cerebellar volumes were not found to vary by disease severity when a "severe ET" sample was compared with a relatively "mild ET" sample and normal controls (disease severity was defined by intention tremor scores for the arms). The authors did incidentally find that despite the more severe ET group being slightly older than the mild ET group, the severe group had relatively *larger* cortical volumes in inferior parietal cortex, the posterior region of the superior temporal gyrus (pSTG), and the parahippocampal gyrus, with right-sided volumes being greater than on the left, when compared to age-matched controls.

These areas of the brain have been shown to play vital roles in spatial processing. The parietal lobes have been implicated as being important for spatial attention and manipulation of mental images, as in mental rotation tasks (Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001; Zacks, 2008). On these types of tasks, individuals must mentally spin or rotate objects to make accurate perceptual judgments. Reversible lesion studies (i.e., using transcranial magnetic stimulation and direct cortical stimulation) have found that the right pSTG is critical for some types of visual search tasks (i.e., serial search for targets perceptually similar to other objects in the array) (Ellison, Schindler, Pattison, & Milner, 2004; Gharabaghi, Berger, Tatagiba, & Karnath, 2006). Lesion and neuroimaging studies have consistently found evidence that the parahippocampal gyrus, especially on the right, is important for spatial memory and navigation (Aguirre, Detre, Alsop, & D'Esposito, 1996; Barrash, Damasio, Adolphs, & Tranel, 2000; Epstein, DeYoe, Press, Rosen, & Kanwisher, 2001). In effect, the areas of cortex that Daniels and colleagues (2006) found to be relatively denser in "severe ET" patients relative to ET patients with milder arm tremor are relatively dorsally located in the brain and have been shown to be important substrates for spatial cognition, including mental rotation, visual search, and spatial memory/navigation. This raises the possibility that patients with severe ET might perform better on spatial tasks measuring these abilities. From a neuroanatomical basis, the findings of Daniels et al. (2006) do not suggest that disease severity is predictive of object/form processing abilities mediated by more ventral occipito-temporal areas, e.g., face processing (see review by Young, De Haan, & Bauer, 2008). As a side note, because mental rotations, visual search, and spatial memory/navigation will be assessed experimentally in this study, more detailed background on these constructs will be provided in a later section of this chapter.

The findings from Daniels and colleagues (2006) also suggest that ET patients with milder arm tremor have less cortical density in spatial processing substrates relative to patients with more severe arm tremor. Their structural data suggest that patients with mild ET would demonstrate measurably worse performance on spatial tasks relative to those with more severe ET. In line with this view, Sahin and colleagues (2006) evaluated a group of newly diagnosed ET patients with milder tremor who had not yet begun medications. Relative to controls, these young ET patients had consistently poor performance across three clinical tasks of visual cognition (i.e., face discrimination, judgment of the orientations of lines, construction of block designs).

Altogether, a positive relationship might exist between intention tremor severity and spatial cognition in ET, as inferred from these behavioral and structural neuroimaging findings. The explanatory mechanism for this relationship remains open to conjecture. It is assumed that the effective coordination of tremulous limb movements in daily life requires effort proportional to the severity of the tremor itself. The positions of the hands relative to objects intended to be used (or avoided) must be tracked continuously during use, and with more severe tremor, more attentional resources would need to be diverted to compensatory cognitive functions, such as spatial computations. Over time, because individuals with severe kinetic tremor of the arms exercise these abilities daily as they compensate for their tremor, it is feasible that their spatial abilities improve measurably, as demonstrated by superior performance on visuospatial tests and greater density in spatial cortex via neuroplastic changes.

Neuroplasticity and Visuospatial Cognition

Neuroplasticity is the brain's ability to undergo structural alterations and functional adaptations in response to internal changes (e.g., CNS injury, disease) or environmental changes (e.g., experience, training, or living with tremor). This mechanism has been proposed to account for such findings as the positive correlation between posterior hippocampal volumes and driving experience / spatial navigation ability in London taxicab drivers (Maguire, Gadian, Johnsrude, Good, Ashburner, Frackowiak, et al., 2000), as well as the reversible effect of only a few months' juggling training on the size of motion-processing areas in visual cortex (Draganski, Gaswer, Busch, Schuierer, Bogdahn, & May, 2004). Neuroplasticity may involve spine density changes or neurogenesis (Grutzendler, Kasthuri, & Gan, 2002; Trachtenberg, Chen, Knolt, Feng, Sanes, Welker, et al., 2002; Kempermann, Kuhn, & Gage, 1997), and in the context of slow-progressing CNS damage (e.g., low-grade gliomas), it is usually associated with complete or near-complete recovery of cognitive functions (Desmurget, Bonnetblanc, & Duffau, 2007). Although the progression of ET symptoms varies individually, ET is generally associated with a slow rate of advancement with marked changes often on the order of decades. Springer and colleagues' (2006) observation of better-than-average visuospatial performance in ET is compatible with these observations.

Moreover, there is evidence that visuospatial functions are among the most functionally plastic and amenable to rehabilitation after brain injury. Cicerone and colleagues' review of 87 cognitive rehabilitation studies found that the most rigorous randomized controlled studies have demonstrated positive and lasting benefits for visual inattention (i.e., hemispatial neglect) and cortical blindness interventions, whereas such evidence is lacking for non-strategy based "executive" skills (Cicerone, Dahlberg, Malec, Langenbahn, Felicetti, Kneipp, et al., 2005). Benefits for training aspects of visual attention have been demonstrated not only for brain injured populations, but for the healthy young and the healthy elderly as well (e.g., Ball, Beard, Roenker, Miller & Griggs, 1988; Ball, Berch, Helmers, Jobe, Leveck, Marsiske et al., 2002; Edwards, Wadley, Myers, Roenker, Cissell, & Ball, 2002; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). Other visuospatial skills appear to benefit greatly from training, such as mental imagery or rotation ability (Lohman & Nichols, 1990). Moreover, it has been established that training effects can generalize or “transfer” to other skills, such as video game training effects on selective visual attention or speed of training effects on instrumental ADLs (Edwards et al. 2002; Green & Bavelier, 2003). The domains of memory and fronto-executive functioning have not shown such amenability to functional plasticity, perhaps accounting for the discrepancy between superior visuospatial functions but mildly impaired fronto-executive functions in severe ET patients (Springer et al., 2006).

Regardless, a synthesis of these ideas suggests that intentional tremor in severe ET may be associated with superior spatial abilities. Functional neuroplasticity is commonly observed in the visuospatial domain of cognition for healthy and brain-damaged individuals, it has been documented with substantial and lasting change in patients well above 65 years of age, and robust maintenance (or improvements) in performance can be observed when damage is subtle in progression, as is observed in ET.

Tremor Severity vs. Tremor Duration: Potential Visuospatial Predictors

The principles derived from the neuroplasticity literature raise the question as to whether tremor severity (i.e., amplitude) or tremor duration might better predict visuospatial performance in ET. Because of individual variability and the overall slow progression of ET severity, these two constructs are not highly correlated in ET (Elble, 2000; Putzke, Whaley, Baba, Wszolek, & Uitti, 2006). It was suggested above that neuroplastic changes may occur in visuospatial cortex as a result of a chronic increase or diversion of attentional resources to visual spatial elements of the environment. The question arises, however, as to whether it is time or the “dose” (i.e., amplitude of the tremor to which patients must adjust) that is associated with the most change. Both are likely necessary, but it is argued here that the dose, or severity of the tremor, is the more important factor. It is likely that the amplitude of the tremor must fall above some threshold level in order to elicit more effortful engagement in visual attentional resources and practice of spatial computational functions. Conversely, because very mild tremor often presents negligible difficulty to the individual, it likely requires little if any functional adjustment. As neuroplastic changes require some internal or environmental change, it is unlikely that very mild tremor would be associated with improvements in behavior or cognition.

Furthermore, it has been established that neuroplastic changes in visuospatial cortex can occur in healthy, younger individuals after only a few months of training (Draganski et al., 2004). This timeline likely is much faster: rats that were trained on a skilled reaching task showed increases in synaptic strength, synapse number, and map reorganization after only several days of training, and this occurred after making significant behavioral gains, as reviewed by Kleim & Jones (2008). Granted, neuroplastic changes are slower with increasing age, but at any given amplitude of tremor to which the individual must adjust, the duration of time after a few years (conservatively) would likely not have as much association with neuroplastic changes as the amplitude of the tremor itself (Kleim & Jones, 2008). This may be the case especially because the rate of progression in ET tends to be slow; significant increases in tremor severity do not occur on the order of months but rather, years or even decades, whereas the rate of neuroplastic changes tend to occur on a much faster scale.

Finally, tremor severity often is a more reliable measure than disease duration. It can be assessed in an entire research sample by a single clinician, whereas disease duration depends on the reliability of each patient’s self-reported history. Many patients report being unaware of tremor symptoms until a doctor notified them of their presence. Other patients report first noticing tremor symptoms but are unable to recall precisely when in their lives this occurred. Thus, estimates often are given with a 5 or 10 year margin of error. Taken together (and the degree to which they can be measured reliably), tremor severity rather than duration of tremor symptoms is likely associated more with changes in spatial cognition and its associated neurological structures (if such associations exist).

Spatial Cognition Subtypes: Foci of the Present Study

As was reviewed above, the structural neuroimaging data of Daniels et al. (2006) indicate that ET patients with more severe upper extremity tremor (relative to those with mild or no tremor) have greater cortical volumes in parietal cortex, posterior superior temporal gyrus, and posterior parahippocampal gyrus (with volumes being larger on the right side). These three areas have been associated with different types of spatial abilities, including mental rotation, visual search (hard-feature serial search), and spatial memory and navigation, respectively. For this reason, individuals with relatively severe ET vs. milder ET might have “neuroanatomical advantages” on these types of tasks and perform measurably better due to compensational differences. This chapter concludes with relevant background on these subtypes of spatial cognition and their measurement in order to provide sufficient background for the present study.

Mental Rotation

"Mental rotation" refers to the ability to spin or rotate mental representations of objects. In the classic mental rotation experiment, Shepard & Metzler (1971) asked participants to compare drawings of three-dimensional geometric stimuli to images of those stimuli rotated about an axis. They were asked to judge whether the second (rotated) stimulus was the same as the first (fixed) stimulus, or whether it represented a mirror image of that stimulus. Results of this study and many others that followed indicated that reaction time for this task increased in linear proportion to the angle of disparity between the rotated object and the fixed object. Moreover, the accuracy of judgments on these tasks decreased as a function of the angle of disparity between the two objects. These findings have been reproduced extensively over the past several decades, and they suggest that mental images in the brain are maintained and manipulated as "topographic wholes."

Functional imaging and lesion studies have provided a wealth of evidence suggesting that the parietal lobe, especially in the right hemisphere, plays an important role in the processes of mental imagery and rotation. For example, parietal activity has been shown to vary positively and parametrically by the difficulty (or distance of) the mental rotation performed (Zacks, 2008). Because Daniels et al. (2006) found parietal regions (especially on the right), to be more cortically dense in severe ET in comparison to milder ET, there may be a neuroanatomical basis for the proposition that severe ET patients might perform better on mental rotation tasks.

Relevant to the present study, mental rotation with *hand-based stimuli* may be a skill in which relatively severe ET patients are especially proficient. In day-to-day life, one's hands are used to interact skillfully with objects in the environment, most often with visual guidance. ET, affecting primarily the voluntary movement of the hands and arms, impairs the ability to interact with objects. It is likely that as a compensatory mechanism of adjustment, severe tremor in ET requires effortful attention and use of spatial skills relating to visuomotor planning and manipulation of the hands. A hand-based mental rotations task seems to be a logical candidate for demonstrating these changes in ET, if they exist.

The use of hands as stimuli in mental rotation studies does change the operating characteristics of these tasks to some degree, however. Traditionally, inanimate geometric objects such as two- and three-dimension block figures are used as stimuli (e.g., Shepard & Metzler, 1971). However, it is now appreciated that people are faster at mental rotation tasks when body parts or tools are used as stimuli, particularly when a head, face, or hand is attached to the stimuli (Amorim, Isableu, & Jarraya, 2006). These findings relate to the concept of "embodiment", the tendency of an individual to imagine that the particular body part viewed is their own. It has been postulated that when the stimulus to be rotated is a tool, such as a hammer, subjects "embody" the tool; they imagine rotating it with their dominant hand as opposed to imagining the object rotating by itself in space (Vingerhoets, Lange, Vandemaele, Deblaere, Achten, 2002). Similarly, when hands are used as stimuli in mental rotation tasks, proficiency increases (i.e., accuracy increases, and response times to generate correct answers decreases) when the hand can be easily imagined as their own (embodied). The easier it is to embody a given stimulus, the more efficiently that stimulus can be mentally manipulated.

Mental representations of body parts are also more easily formed and manipulated when those body parts are viewed in anatomically possible positions. In other words, mental imagery of embodied objects (e.g., hands) is subject to actual biomechanical constraints. The results of studies using mental rotation tasks with hand-based stimuli show that higher error rates and slower response times for correct answers occur in conditions whereby the hand stimuli are viewed at angles that are difficult to produce in reality (e.g., viewing the back of one's own hand with the fingers pointing down) (Amorim et al., 2006). Speed of rotation is faster and accuracy is higher when hand stimuli match more natural positions (e.g., a view of the back of the hand with the fingers facing away from the body). For these reasons, images of rotated hands are harder to mentally rotate when they are presented at certain angles of rotation relative to the reference point. The specific task used in the present study is described in the Methods section (Chapter 4).

Visual Search

Visual search is an intrinsic and vital part of everyday experience for non-visually impaired people. Finding particular objects by sight might be an especially important skill for individuals with severe ET. For example, an increased awareness of objects' locations nearby might be necessary for avoiding accidents or injury or damage to the objects themselves resulting from motor control difficulties. Visual search occurs relatively automatically or with more sustained effort. For example, if an object has a very distinctive feature, it might visually "pop out" of the scene to capture one's immediate attention, as in spotting a red cardinal in the snow among several sparrows.

If an object is located in the midst of objects that share more visual features, then it might be found only after relatively effortful, serial searching (e.g., finding one’s house key among other keys on the ring).

Visual search tasks have been developed to study these and other attention phenomena both clinically (as in the assessment of hemispatial visual neglect), and experimentally (as in understanding the neural basis of automatic vs. controlled types of visual attention). They are administrated in a standardized format using well-defined stimuli, usually arranged on a sheet of paper or a computer screen. Two types of visual search tasks were described by Treisman and Gelade (1980): feature search tasks, whereby the target object is defined by a distinct visual feature (e.g., red, in the cardinal example), and conjunction search, whereby the target object has a unique combination of features shared by other objects in view (e.g., the key, which might be nickel among other nickel and brass keys but have a unique pattern of holes on the grip).

The neural correlates of visual search typically include the parietal cortex but also depend on the parameters of the visual search task, such as whether attention is overt or covert, or whether the target has predefined features or merely visually distinct from other objects in some way. In the present study, a “hard-feature, serial exploratory search” task was selected because of its reliance on the superior temporal gyrus (STG), a structure shown to be relatively more dense in severe ET vs. mild ET (Daniels et al., 2006). The role of the right STG on one particular hard-feature search task was demonstrated in two experimental studies. First, Ellison and colleagues (2004) used a stimulation-induced reversible lesion method (trancranial magnetic stimulation) on subjects performing various bisection and visual search tasks. A double dissociation was demonstrated: performance on the hard feature-based serial search task (but not bisection tasks) was impaired when right STG was stimulated, while impairment was evident on bisection tasks (but not the visual search tasks) when the right PPC was stimulated. The right STG was critical only for the hard-feature visual search task, but no performance reductions were found on simple-feature or hard-conjunction visual search tasks. Gharabaghi, Berger, Tatagiba, and Karnath (2006) supplemented these findings using direct cortical stimulation of the middle-right STG. This group showed that intra-operatively, performance accuracy dropped from near-perfect to chance levels on a modified version of Ellison and colleagues' (2004) hard-feature search task. No decrement in performance was found with stimulation to other adjacent areas, however, including the right PPC. These findings suggest that the right STG is uniquely important for hard-feature serial visual search. Severe ET patients might be better on this type of task compared with those with milder ET, as the right STG was found to be larger in relatively severe ET. The hard-feature serial search task used in the present study is described in the Methods section (Chapter 4).

Spatial Memory and Navigation

The ability to find one's way to remembered locations is a vital part of everyday functioning and critical to independent living. When this ability is impaired, as is often the case in early dementia, people may exhibit wandering and getting lost in familiar places (Klein, Steinberg, Galik, Steele, Sheppard, Warren et al., 1999). A spatial navigation / memory task was chosen for the present study because some of the neural correlates for spatial navigation were found to be greater in relatively severe ET vs. milder ET (Daniels et al., 2006). Although it may not be immediately clear as to why severe ET would show an advantage in this skill beyond this reason, further discussion of spatial navigation deserves merit to provide context to the present study.

Our understanding of spatial memory and navigation has been informed by a vast literature from animal and human studies. One particularly informative experimental method that comes from the animal literature is the Morris water maze task (Morris, 1981, 1984). In this task, rats are placed into a circular pool of opaque water and trained to find a submerged (invisible) platform. When the platform is located in a fixed position, rats find it efficiently, even when released from different locations. Morris (1981; 1984) explained the rats' behavior as the consequence of using allocentric strategies, i.e., identifying the position of the platform with respect to its relative position to visual cues outside the pool (the walls of the pool itself had no distinguishing features).

The Morris water maze task has been adapted into computerized versions, allowing spatial memory and navigation to be studied in humans in a pragmatic way. One example is the Computer-Generated Arena (Thomas, Hsu, Laurance, Nadel, & Jacobs, 2001). Like the Morris water maze, this particular task also contains a pool of water within a square room, distal cues, and an invisible target, but these elements are displayed virtually in first-person view on a computer monitor. The test subject "navigates" about the pool by using a joystick or the keyboard to simulate intended movement, and the first-person view changes according to these movements. This paradigm has been shown to be a practical, reliable, and low-cost method that has successfully replicated the animal literature based on the original Morris water maze.

Animal and human data from lesion, stimulation, imaging, and cell recording studies have characterized the neural correlates of spatial navigation. Parietal cortex appears to process visual information in terms of body-centered coordinates. Construction of “egocentric” spatial reference frames may be used to guide locomotion on spatial navigation tasks from a first-person point of view (e.g., Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000). More vital to spatial learning and memory, however, is the hippocampus, which appears to play an integrated role in the processing and storage of allocentric spatial information (i.e., locations relative to a spatial reference frame outside the individual) (Ekstrom, Kahana, Caplan, Fields, Isham, Newman et al., 2003; Gron et al., 2000; O’Keefe & Dostrovsky, 1971). Functional impairment of the hippocampus leads to memory deficits on a variety of maze learning tasks (Morris, Garrud, Rawlins, O’Keefe, 1982), including the Computer-Generated Arena (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002). The posterior parahippocampal gyrus often called the “parahippocampal place area” has been shown in many neuroimaging studies to respond preferentially to scenes (images containing information about the layout of a space), rather than other visual material such as objects or faces (Epstein & Kanwisher, 1998; Ekstrom et al., 2003; Gron et al., 2000).

A version of the Computer-Generated Arena task was chosen for the present study because some of the neural correlates for spatial navigation (e.g., parahippocampal and inferior parietal lobe areas, with an apparent rightward asymmetry) were found to be greater in relatively severe ET vs. milder ET (Daniels et al., 2006). Thus, from a neuroanatomical perspective, it might be predicted that severe ET, relative to milder ET, would demonstrate better performance on this task.

CHAPTER 3
SUMMARY OF THE PROBLEM, SPECIFIC AIMS, AND HYPOTHESES

Summary of the Problem

While the emerging cognitive literature in ET has provided fairly consistent evidence for mild frontal-executive functioning deficits, visual cognition has been characterized much more variably. This inconsistency may relate to (1) methodological limitations or variance among studies, among them being a failure to distinguish between spatial and object/form subtypes of visual processing, and (2) tremor severity as a potential positive predictor of spatial abilities. First, methodological problems in the cognitive literature in ET relate largely to possible confounds creating a bias toward describing visuospatial deficits. For example, many visuospatial tasks have a motor component requiring coordinated dexterity of the hands (e.g., WAIS-III Block Design, Rey-Osterrieth Complex Figure). Some individuals with ET might perform poorly on these tasks because severe tremor may prevent effective manipulation of small blocks or a pen. Other studies did not fully detail or use appropriate screening methods for general cognitive impairment. Thus, it is unclear as to whether the ET patients used in these studies were adequately assessed for factors that would account non-specifically for visuospatial problems, such as dementia, severe medical conditions, traumatic injury to the brain, or psychiatric impairment.

Aside from methodological flaws, another reason why visual cognition in ET has been difficult to characterize may relate to a failure for studies to dissociate between “spatial” and “object/form” subtypes of visual processing. The literature historically has distinguished between these two modes of visual processing and shown their dissociation in function (i.e., cognitive performance) and neuroanatomical damage. A review of the cognitive and structural neuroimaging ET literature suggests that individuals with ET may be more likely to perform better on tasks requiring spatial perception or judgments, rather than on tasks whereby performance is more heavily mediated by visual feature/form processing.

Finally, neuropsychological studies of ET have paid little attention to studying factors contributing to spatial cognition in this population. This is possibly because most of the cognitive literature in ET has focused on fronto-executive functioning. Recent structural neuroimaging findings by Daniels and colleagues (2006) showed that a subgroup of ET with more severe and slightly more longstanding arm tremor had relatively denser areas of dorsal-parietal cortex (right > left) traditionally associated with spatial cognition (e.g., mental rotation, visual search, and spatial navigation). The superior spatial performance in ET shown by Springer and colleagues (2006) was also found in a relatively severe (pre-surgical) ET population; this behavioral data appears to complement the structural neuroimaging findings of Daniels et al. (2006). It is suggested that spatial skills may be “exercised” more in severe ET because of the cognitive compensation required to functionally adjust to this limitation in order to perform daily activities. This may contribute to improved spatial skills and more robust areas of cortex that mediate these skills.

The overall goal of the present study was to further investigate and test the validity of this paradoxical relationship between disease severity and spatial cognition in ET. A purely cognitive (behavioral) approach (and not a neuroimaging approach) was taken in this study as a first step. Various types of visual cognitive tasks were used under the assumption that the spatial vs. object/form visual cognition was an important theoretical distinction, and that subtypes of spatial cognition might have different operating characteristics in this population. The spatial tasks were also chosen in order to target a potential neuroanatomical advantage in severe ET, as was suggested by the structural imaging data by Daniels et al. (2006). The specific aims of the study are outlined here, with the next chapter describing the methods used to carry them out.

Specific Aim 1

Overview

This study sought to use cognitive testing as a first step in examining and characterizing visual cognition in ET, using methodologically rigorous methods. Tasks were selected based on theory derived from cognitive neuroscience research, as well as previous findings from cognitive and structural neuroimaging research. Both clinical neuropsychological tasks and timed, computerized experimental tasks were used.

Hypotheses

In the first specific aim of this study, it was hypothesized (paradoxically) that relative to controls, patients with more severe ET (measured by upper extremity tremor) have better spatial skills than those with less severe disease. It was further hypothesized that the severity of ET (high or low) does not have any relationship with visual cognitive skills that are based more on efficient recognition or discrimination of shapes and forms. These tasks were included as control tasks to establish specificity of the superiority effect primarily to the spatial domain only. This study was designed to test these hypotheses while accounting for important methodological variables that sometimes have limited the findings of previous studies, e.g., appropriate screening methods for generalized cognitive impairment.

Predictions

It was predicted that a group of severe ET patients (i.e., those with relatively high-amplitude tremor) would demonstrate superior performance on spatial cognitive tasks relative to an ET group characterized by milder tremor. These spatial tasks involved the judgment of the orientation of lines, mental rotations of hands, visual search, and spatial memory/navigation. No group differences were predicted on object/form tasks, i.e., facial recognition or object-based feature discrimination. Neither ET group was predicted to outperform a group of normal controls.

Analyses

These predictions were tested via analysis of variance (ANOVA) or its non-parametric equivalent (i.e., Kruskal-Wallis), using a between-subjects factor of group (mild ET, severe ET, controls). Various within-subjects factors (mixed-models ANOVA) allowed for the testing of condition-specific effects by task. Analyses incorporated statistical assumption testing and made appropriate adjustments when necessary, as detailed further at the end of the methods section.

Specific Aim 2

Overview

The second aim of this study, if necessary, was designed to address and rule out other potential factors underlying any demonstrated spatial superiority effect, in order to more rigorously determine the impact of tremor severity on spatial functioning and identify the most influential contributor of any spatial superiority in severe ET. That is, the contribution of disease severity to spatial abilities in the entire ET sample was to be tested, above and beyond other sociodemographic, fronto-executive, and mood predictors. No study specifically has examined the relationship between visual cognition and other variables in ET patients.

Hypothesis, Prediction, and Analysis

In the second aim of this study, it was hypothesized that greater upper extremity tremor is predictive of better spatial abilities, even after accounting for other correlates of spatial functioning (e.g., age, measures of fronto-executive functioning, gender, etc.). After combining the mild and severe ET groups from the first specific aim into one sample, it was predicted that upper extremity tremor would positively predict better spatial functioning (JOLO, mental rotation of hands, visual search, spatial memory/navigation), above and beyond other predictor variables. Spearman correlations were used initially to identify correlates of test-specific spatial performance in ET, for variables whereby a spatial superiority effect was found (i.e., severe ET outperforming mild ET). These were entered in separate stepwise regressions along with the tremor severity variable in order to determine which measures significantly predicted spatial performance. Tremor severity was then tested as a significant predictor of spatial functioning above and beyond any other predictor variables using hierarchical regression, with all other predictors held constant in a first model, and tremor severity entered into a second model. Final regression models were tested for outliers and meeting statistical assumptions.

CHAPTER 4
MATERIALS AND METHODS

Design Overview

An overview of the testing session procedure is provided in Figure 4-1. As shown, individuals with ET and healthy controls were recruited and screened for various inclusion/exclusion criteria and then underwent a brief neuropsychological battery of attention-working memory, executive (set-shifting, speeded fluency), and reaction time tasks. This battery was followed by clinical and experimental tests of visual spatial and object/form processing. The entire testing procedure took approximately 3-4 hours per participant and was conducted at either the Cognitive Neuroscience Laboratory at the University of Florida (UF) McKnight Brain Institute or at the participant's residence (provided that an adequate and quiet testing environment was available).

Approximately equal numbers of participants were tested at home and in the lab, in both the ET and control participant groups. Following completion of the study, participants received $20 in cash and reimbursement for any parking expenses accrued on the UF campus ($3). This study was funded by the American Psychological Foundation (2007 Benton-Meier Neuropsychology Award). Recruitment, exclusion criteria, and testing procedures are described in more detail below.

Participants

Recruitment and Initial Inclusion Criteria

A total of 70 individuals (N=36 ET, N=34 Normal controls) between the ages of 50 and 85 years were recruited and completed testing[1]. To be included in the ET group,

[1] Another eight normal controls between the ages of 30 and 50 were tested but were not included in the present study, as no individual with ET who was recruited into the study fell into that age range.

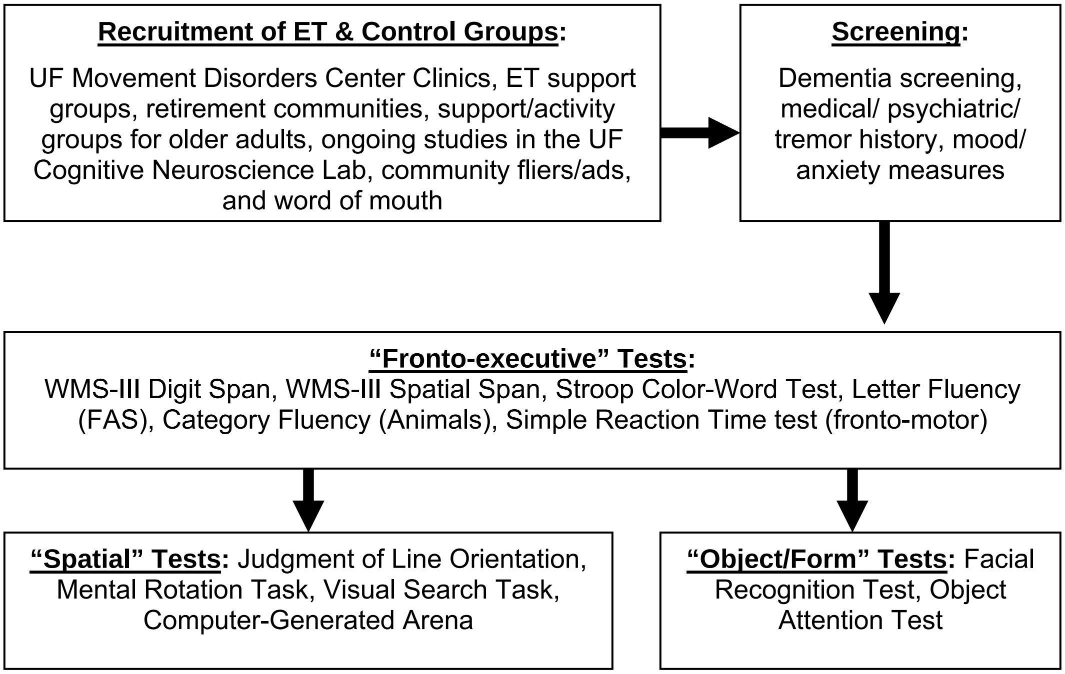


Figure 4-1. Overview of the testing session procedure.

participants were required to have (a) a clinical diagnosis of ET by a neurologist, with the primary sign being bilateral and persistent kinetic tremor of the hands and forearms (Deuschl, Bain, & Brin, 1998), and (b) a stable ET treatment regimen for at least one month prior to testing. Participants were assigned to the healthy control group on the basis of a negative history of tremor and falling within the age range of the ET patient group.

Participants were recruited from several sources in north-central Florida. For ET participants (total N=36), this included the UF Movement Disorders Center Clinics (N=21), ET support groups (N=9), Oak Hammock retirement community in Gainesville, Florida (N=3), and via community fliers/advertisements and word-of-mouth (N=3). Fourteen of the ET participants were candidates for deep brain stimulation through the UF Fast Track program. Control participants (total N=34) were recruited from retirement communities in north central Florida (N=12), a local support and activity group for older adults (N=8), ongoing studies in the UF Cognitive Neuroscience Lab (N=6), community fliers/advertisements and word-of-mouth (N=6), and an ET support group (N=2).

Screening and Exclusion Criteria

After being recruited into the study, participants provided written informed consent and then were assessed for inclusion/exclusion criteria. ET exclusion criteria were as follows: (1) tremor that was unrelated to ET (e.g., sudden-onset, drugs, anxiety), is task-specific (e.g., writing only), or characterized by sudden onset or stepwise progression, (2) report of other abnormal neurological signs or disease (e.g., dystonia, Parkinson’s disease), (3) history of moderate or severe brain injury, e.g., traumatic injury with a loss of consciousness greater than 30 minutes, neurosurgical interventions involving resection/ablation, history of stroke, (4) current uncontrolled medical illness that could potentially affect cognition (e.g., cardiac or pulmonary disease, hypothyroidism, cancer, HIV), (5) failing screening for basic vision and cognitive impairment / dementia, as outlined below, (6) diagnosis of self-report of significant learning disorder or ADHD, or less than a ninth grade education, and/or (7) a history of substance abuse or "heavy" alcohol intake[2]. Exclusion criteria for controls included: (1) evidence of ET (i.e., exhibited or reported a history of tremor) or (2) meeting any of the exclusion criteria for the ET group.

Tremor symptoms were assessed using the Fahn–Tolosa–Marin Tremor Rating Scale (TRS; Fahn, Tolosa &, Marin, 1993). This standardized measure was administered in order to document the presence and severity of tremor in the ET group and the absence of tremor in the controls. The TRS is comprised of several subscales that measure three types of tremor (resting, postural and kinetic) in various regions of the body (e.g., head, arms, legs, etc.), and on various tasks and activities of daily living (ADLs). A scale from 0 (non-existent) to 4 (severe) is used for each rating of tremor or impairment level. The range of possible scores on the TRS is 0 to 144. In the present study, the primary measure of tremor severity was postural/kinetic tremor of the upper extremities (average of left and right scores). Severity scores were also calculated for axial tremor (head, face, tongue, voice, and trunk), and tremor-related disability in activities of daily living (speaking, eating, drinking, hygiene, dressing, writing, and working). The TRS is reproduced in Appendix A.

To screen for dementia, all participants received a brief cognitive screening measure called the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh,

[2] Heavy alcohol intake: defined by the National Institute on Alcohol Abuse and Alcoholism in the past year (>14 drinks per week for men and >7 drinks per week for women; http://www.niaaa.nih.gov/).

1975), a recent memory task involving immediate and delayed recall of novel stories (Logical Memory subtests from the Wechsler Memory Scale, Third Edition [WMS-III]; Wechsler, 1997b), and a measure of confrontation naming (the Boston Naming Test [BNT]; Kaplan, Goodglass, & Weintraub, 2001). Individuals who scored below 26 on the MMSE or below the 5th percentile on either the immediate or delayed recall portions of the Logical Memory subtest or the BNT were excluded from the analyses[3].

A total of six individuals who completed testing were removed after exclusion criteria were applied. They included four males and one female from the ET group, resulting in a final sample size of 31 ET participants (16 males, 15 females). A male control subject also was excluded, resulting in a final sample of 33 control subjects (15 males and 18 females). Thus, the final sample used in the statistical analyses consisted of 64 participants (31 ET, 33 controls). The specific reasons for exclusion are shown in Table 4-1.

Participant Characteristics

The ET sample (N=31) was divided into "severe ET" and "mild ET" subgroups in order to test the hypothesis that individuals with severe vs. mild ET differ relative to controls on spatial visuoperceptual tasks (but not object/form visuoperceptual tasks). At present, there are no standard criteria for distinguishing between "mild" and "severe" subgroups in ET. In this study, "mild" and "severe" ET subgroups were defined on the basis of individual upper extremity tremor scores (i.e., an average of postural/kinetic upper extremity tremor scores on the TRS for the right and left hands). This measure

[3] One participant with ET scored 25 on the MMSE; however, an item analysis revealed that he lost two points due to an illegible written sentence and illegible intersecting pentagons (related to his tremor). His Logical Memory and BNT scores were well within the average range, and therefore, he was not excluded from the study.

Table 4-1. Rationales for exclusion of participants by group, sex.

Group	*Sex*	*Rationale for exclusion*
Control	Male	History of learning disorder (reading, spelling)
	Female	None excluded
ET	Male	History of learning disorder (reading) Scored in the impaired range: WMS-III LM-I & LM-II History of seizures
	Male	Heavy drinking (6 beers/day) Marijuana use (2x/week)
	Male	History of stroke reported
	Male	< 9 years of formal schooling (6 years) Untreated diabetes
	Female	History of bilateral craniotomies & aneurysm treatment

Note: WMS-III=Wechsler Memory Scale, Third Edition; LM = Logical Memory was chosen instead of overall tremor severity because the study hypotheses were based on upper tremor severity rather than tremor from other sources (e.g., vocal tremor would factor into a total TRS score, but would lack a feasible mechanism for improving spatial ability). The median score was calculated and used as the dividing line to form “severe ET” and “mild ET” subgroups. Figure 4-2 shows the distributions of the upper extremity tremor scores for the two subgroups. Table 4-2 provides group statistics concerning sociodemographic and clinical characteristics. First, one-way ANOVAs and chi-square tests were performed to compare the ET groups and controls on sociodemographic variables. There were no group differences in age, gender ratio, education, handedness or the Barona full-scale IQ estimate, ps > .2. Next, the two ET groups alone were compared on indices of disease severity (t-tests) to test to what extent the “mild” vs. “severe” distinction held across multiple measures of disease severity. Several significant differences were found in the expected direction, beyond the total upper extremity tremor variable upon which the two groups were defined, $t(16.23) = -5.72$, $p < .001$, $r = .82$; severe ET group > mild group. Specifically, the severe ET group scored higher than the mild ET group on measures of upper right extremity tremor, $t(15.95) = -5.45$, $p < .001$, $r = .81$, and upper left extremity tremor, $t(17.31) = -4.80$, $p < .001$, $r = .76$, axial tremor, $t(20.26) = -2.50$, $p < .05$, $r = .49$), the total TRS score, $t(15.22) = -6.33$, $p < .001$, $r = .85$, and ADL impairment, $t(21.73) = -6.15$, $p < .05$, $r = .85$. The severe and mild ET groups did not differ by age of tremor onset or the duration of tremor (ps > .2). Individuals from the mild ET group, however, were diagnosed with ET more recently than those from the severe ET group, $t(20.54) = -2.54$, $p < .05$, $r = .49$. The proportion of severe ET and mild ET participants on tremor-

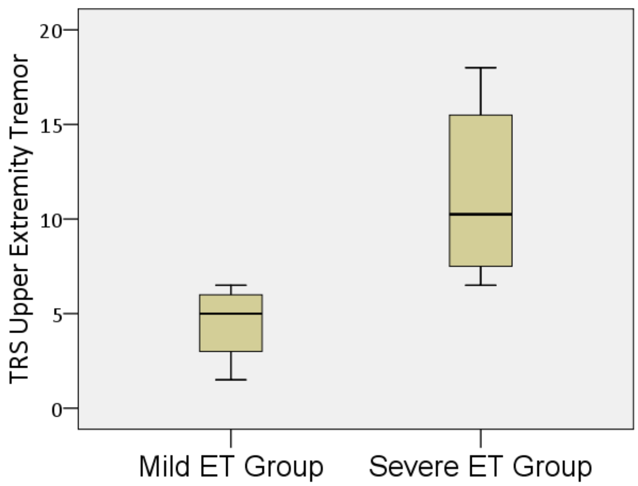


Figure 4-2. Upper extremity Tremor Rating Scale (TRS) score distributions for the mild essential tremor (ET) and severe ET groups. Range: 0-20.

Table 4-2. Demographic and other characteristics by group

Demographic characteristic	*Control*	*ET mild*	*ET severe*
N	33	16	15
Sex ratio, Female:Male	18:15	9:7	6:9
Age, years	71.3 (7.5)	73.1 (9.5)	69.8 (7.6)
Education, years	15.6 (2.7)	15.4 (3.0)	14.3 (2.3)
Barona Full-Scale IQ Estimate[4]	111.8 (6.3)	109.5 (7.0)	108.8 (5.6)
Handedness, Right:Left	30:3	14:2	13:2
ET-specific characteristic	*Control*	*ET mild*	*ET severe*
Years since onset of tremor	--	15.3 (16.3)	19.9 (13.5)
Years since diagnosis	--	5.3 (4.4)	11.6 (8.6)*
Age at onset (years)	--	57.8 (18.6)	49.9 (17.1)
TRS, Total Tremor[a]	--	16.1 (6.0)	48.6 (17.3)*
TRS, Axial Tremor[a]	--	0.6 (1.3)	2.3 (2.3)*
TRS, Upper Extremity Tremor[a,b]	--	4.5 (1.6)	11.3 (4.2)*
TRS, ADL Impairment[a]	--	5.5 (3.2)	15.1 (5.0)*
Tremor Medication (Yes:No)	n/a	9:7	11:4
DBS History (Yes:No)	n/a	0:16	3:12

Note: Values expressed in means (SD) unless otherwise indicated. TRS = Tremor Rating Scale, ADL = activities of daily living, DBS = Deep Brain Stimulation.
[a] Score obtained in the "on" medication state (if applicable).
[b] Average score for left and right hands
* Severe ET group score > Mild ET group score (*p*<.05).

[4] Barona, Reynolds, & Chastain (1984)

reducing medications did not differ, $\chi^2(1) = 0.99$, $p = .32$. Three members of the severe ET group underwent DBS surgery compared with none in the mild ET group. In sum, the controls and the severe and mild ET groups were matched on demographic (age, gender ratio, education, FSIQ estimate, handedness) and mood variables. The severe ET group scored higher on all tremor severity measures relative to the mild ET group.

Fronto-Executive Functioning Tests

Overview and Rationale

After the initial screening and data collection, all participants completed a subset of tasks that have been associated with functioning of frontal-executive systems. These included tasks of attention/working memory, cognitive inhibition, and speeded word generation. There were several reasons for administering these tasks. First, analyses were planned to determine whether these types of "fronto-executive functioning" might be associated with performance on visuospatial tasks. Second, a variety of studies have consistently described mild deficits in fronto-executive functioning tasks in ET. As such, a similar profile would be expected in the current sample of ET patients. Finally, the tasks used in the present study were also selected specifically because they did not require a hand-based motor response (which would be susceptible to upper-extremity tremor-related interference). The tasks are described in more detail below.

Tests of Working Memory / Attention

"Digit Span" subtest

This subtest of the Wechsler Memory Scale-Third Edition (WMS-III; Wechsler, 1997b) is a measure of auditory attention and mental manipulation. Strings of numbers are read by the examiner in increasing length. Participants were required to repeat the strings exactly as they were presented (attention condition), and in a second section, to repeat them in backward order relative to how they were presented (manipulation condition). Performance was converted to standardized scores using comparison to a normative sample matched by age.

"Spatial Span" subtest

This subtest of the WMS-III is a visual analog of the Digit Span subtest. The experiment uses a finger to touch increasingly long sequences of blue cubes (ten of which are affixed in a roughly evenly distributed arrangement over a white board). Participants must touch the same sequence of blocks in the same order as the experimenter (attention condition), and then in a subsequent section, in the reverse order as they were presented (manipulation condition). Again, age-matched norms from the WMS-III scoring manual were used to convert scores to a standardized metric (Wechsler, 1997b).

Test of Inhibition: "Stroop Color and Word" Test

On the Stroop Color and Word (Stroop CW) test (Golden, 1978), one must name the colors of ink in which a list of words is printed (i.e., "red", "blue", and "green"). The words themselves are the names of colors (i.e., "red", "blue", and "green"). Because the color and word never match for any given item, participants must inhibit the relatively automatic behavior of reading the words themselves in order to correctly name the incongruent color of the ink in which the word is printed. Performance is measured in terms of the number of correctly named colors in 45 seconds (Interference condition). Two other "baseline" trials are administered as well for comparison to performance in the interference condition: in the first, participants simply read a list of color names printed in black, and in the second, they must name the different colors of ink in a series of printed "XXXX"s. Age corrections are applied to the raw scores. The corrected raw score for the interference trial (administered third) was used as a measure of “inhibition” in this study.

Tests of Verbal Fluency: “Letter Fluency” & “Category Fluency” Tests

A letter fluency test and a category fluency test were used in this study to provide measures of verbal fluency / word generation using lexical/letter (F, A, S) and semantic (animals) rules for word generation, as described by Spreen and Benton (1977). Verbal output over one minute is measured for each condition, providing a total score representing letter fluency and a total score representing category fluency. Standardized scores are calculated from these scores using demographically corrected norms (Heaton, Miller, Taylor, & Grant, 2004).

Visual Cognition Tests

Overview & Rationale

A battery of clinical neuropsychological tests and computerized experimental tasks was constructed to test two subdomains of visual cognition in ET: spatial cognition and object/form cognition. The “spatial” tasks included one commonly used measure in clinical settings (Judgment of Line Orientation) and three experimental tasks: Visual Search Task, Mental Rotations Task, and Computer-Generated Arena. The “object/form” tasks again included one commonly used clinical measure (Benton Facial Recognition Test) and one experimental task (Object Attention Task). All the experimental tasks were administered on a computer. These tests are described in more detail in the sections that follow.

Clinical Neuropsychological Tests

“Judgment of Line Orientation” (JOLO) test

Benton’s Judgment of Line Orientation (JOLO) test (Benton, Hamsher, Varney, and Spreen, 1983) requires participants to identify the angular orientations of lines using a reference array of 11 different radii arranged in a semicircle. Each of 30 items are worth one point each and contain two lines whose spatial relationships are to be judged (the point is lost if the answer is incorrect for either line). The JOLO was administered for two purposes: to replicate the previous finding of high spatial performance in most of the severe, presurgical ET patients tested in a previous study (Springer et al., 2006) and to provide a clinical measure of spatial perception to be used as evidence for or against a “visuospatial superiority effect”. Raw scores were converted into percentiles relative to a normative population, after adjustment for gender and age (Benton, Sivan, Hamsher, Varney, & Spreen, 1994).

“Facial Recognition Test” (FRT)

On the Facial Recognition Test (FRT; Benton, Sivan, Hamsher, Varney, & Spreen, 1994), participants must match a target individual (photograph of a face) to faces in an array of six, similar-looking people. There are three conditions, whereby the subject must (1) select one face in the array that matches identically to the target face, (2) select three faces shown in front and three-quarters views that match the identity of the target individual, and (3) select three faces shown under unusual lighting conditions that match the identity of the target individual. Answers are reported verbally, referencing photos by number, or by pointing. There are 27 trials on the short form, and scores range from 0 to 27. This raw score is converted to a long-form equivalent score, which is then adjusted for age and years of education completed (Benton, Van Allen, Hamsher, & Levin, 1978).

Computerized Experimental Tasks

Common physical setup across tasks

Each of the three experimental tasks was administered on a laptop computer (Intel® Core™2 Duo CPU T7250 at 2.00 GHz, 2.00 GB RAM). Stimuli were displayed on a 14” monitor with a 1280x800 pixel resolution. While computerized testing in the elderly may raise concerns about whether familiarity with computers may influence cognitive testing, these potential concerns were thought to be outweighed by several advantages: (1) the management of stimuli presentation using precise timing parameters; (2) the ability to incorporate dynamic (and/or more ecologically valid) visuospatial stimuli that are impossible to present using paper-and-pencil-type tests (e.g., a changing, first-person perspective of a 3-D virtual room); (3) the ability to precisely and reliably measure response time data; and (4) efficient computation and management of participant data with secure, password-protected storage.

Responses were recorded using one of two input devices, depending on the task: a handheld videogame control pad, or a customized “button box”. Both are depicted in Figure 4-3. The navigation pad was held in both hands (not affixed to the table or computer) and operated by the left thumb. During C-G Arena pilot testing, it was found that ET patients were able to navigate with greater ease using the control pad compared with a joystick control or the arrow keys on the keyboard. The interfering effects of tremor on the use of the game controls were minimized because the entire navigation pad moved synchronously with any tremor, and thumb-related tremor tended

(A) (B)

Figure 4-3. Input modalities for the computerized tasks. (A) A “button box” was used for four of the experimental tasks. The two “target” buttons with the hand positioning is shown. (B) A handheld, gaming navigation pad was used to operate the Computer-Generated Arena, with navigation controlled entirely by the left thumb as shown (the other buttons had no functionality).

to be minimal. For these reasons, the handheld videogame navigation pad was used for the C-G Arena Task in place of the standard joystick control or arrow keys.

The button box consisted of two large, plastic circles (diameter approximately three inches) mounted to a black tray that was overlaid on the computer keyboard. The right button was dull green in color, and the left button was white. This color coding allowed for precise differentiation between buttons. All subjects responded with their right hand on the right button, and left hand on the left button. The button box was used to record accuracy (i.e., correct, incorrect) and response time (seconds, with accuracy to the hundredths place) in the following computer-based tasks: Mental Rotations Task, Visual Search Task, Object Attention Task, and a Choice Reaction Time task. For these four tasks, stimulus presentation and response collection were controlled by customized software written in Visual Basic 6.0.

Throughout testing, participants were allowed to sit in such a way that they could reduce the amplitude of any tremor throughout the experiment (usually, with their forearms resting on armrests and the edge of the table). Based on pilot testing, ET patients with mild to moderate upper extremity tremor appeared to accurately and efficiently respond using the button box or the navigation pad. Even so, an additional attempt was undertaken to empirically assess each participant’s efficiency in using motor controls. This was done via a Choice Reaction Time task using the button box and via a motor control task using the navigation control pad. Each participant was also interviewed and provided ratings regarding difficulty of use and comfort with the controls during computerized testing.

“Choice Reaction Time” (CRT) task

Rationale. This task was used as a basic “motor speed” task to test potential group differences in simple motor speed when using the manual computer buttons (i.e., mild ET vs. severe ET vs. normal controls in left- and right-handed visuomotor reaction time). At least one previous study (Kumru, Begeman, Tolosa, & Valls-Sole, 2007) found no differences in simple manual RTs between elderly ET patients and elderly controls. It was important to determine whether a similar effect existed in the present sample, as any significant RT differences found between groups could impact interpretation of the RT data extracted from the tasks that used this input device (i.e., the Visual Search Task, Mental Rotations Task, and Object Attention Task).

Stimuli and procedure. Two stimuli were used on the CRT: the word “RIGHT” with a large white arrow below it pointing right, and the word “LEFT” with a large white arrow below it pointing left. The stimuli are shown in Figure 4-4. The word and arrow were presented simultaneously for each stimulus. Each of the two stimuli was presented 10 times, intermixed in one of two pseudorandom orders, for 20 total trials. Participants were instructed to press the left button of the response box with their left hand as soon as they recognized the word “LEFT”, or the right button with their right hand as soon as they recognized the word “RIGHT”. Each trial began with the appearance of the word/arrow stimulus, located centrally on the computer screen. The stimulus remained visible until the participant responded with a left-button press (using the left hand) or a right-button press (using the right hand). Response times were recorded to the nearest hundredth of a second and recorded “correct” if the stimulus direction matched the side of the response. Mismatches were coded as “incorrect.” The next trial began after a random interval of 2-4 seconds.

(A) (B)

Figure 4-4. Choice Reaction Time (CRT) task stimuli. (A) The “left” stimulus, requiring a speeded button press with the left hand on the left button. (B) The “right” stimulus, requiring a speeded button press with the right hand on the right button.

Data reduction. Median RTs were computed separately for the left and right hands over correct trials (Ratcliffe, 1993). Incorrect trial data were not used. Thus, two dependent variables were extracted for each participant: "Left RT" and "Right RT".

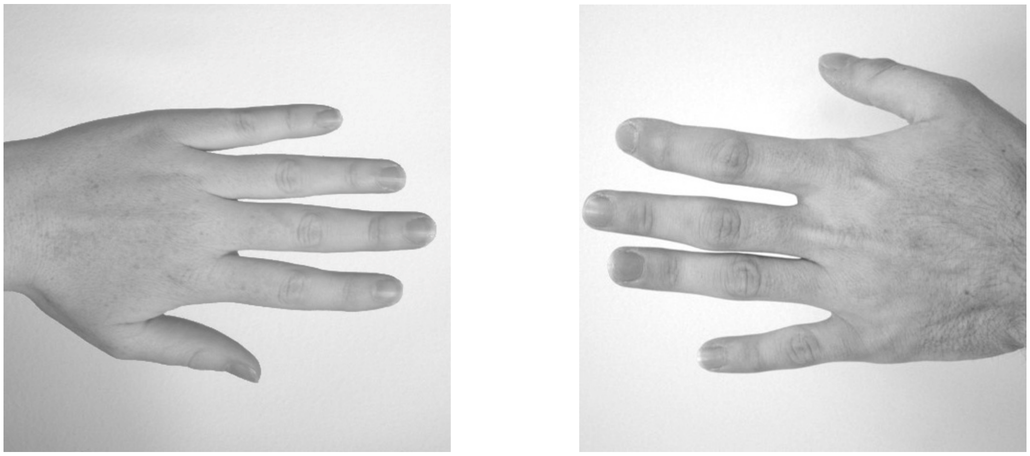
"Mental Rotation Task" (MRT)

Description. The paradigm used in the present study was modeled after Funk and Brugger (2007) and used single photos of hands rotated in 2-dimensions (i.e., with the plane of the page, like the spinning of a needle in a navigational compass). When using and viewing one's own hands to interact with objects skillfully in the nearby environment, with or without visual guidance, spatial abilities undergo use. Potentially, this may amount to a measurable "practice effect" of spatial elements of visual cognition specifically related to the hands. This practice effect would occur with hands to a higher degree than with objects because greater experience with hands as stimuli increase the ease with which mental representations of hands can be created (Bethell-Fox and Shepard, 1988). Moreover, as ET most often affects the intentional movement of the hands and upper extremities, this ability may be practiced more often particularly in this population. For these reasons, hand stimuli were incorporated in this mental rotations task.

Stimuli. Stimuli were created using two different actors: one male and one female. For each actor, one picture of the right hand in the dorsal view (fingers outstretched) was taken to create two core stimuli (one male right hand and one female right hand), from which the rest of the stimuli were derived. The photos were taken in black and white under similar lighting conditions and backgrounds (a featureless wall). First, left versions of the right male and female hands were created by horizontally flipping them in a digital image editor. Each of these four stimuli (male-right, male-left, female-right, female-left) were used to create sets of four stimuli representing four angles of rotation: fingers pointing to the top of the image (0 degrees), rotated 90 degrees to the right, upside down (rotated 180 degrees), and rotated 270 degrees to the left. Only these 4 orientations were used in order to keep test time to a minimum. Thus, the final stimulus set consisted of 16 unique hand stimuli: 2 actors (male/female) X 2 hands (right, left) X 4 positions (0, 90, 180, 270 degrees), and the eight stimuli from each actor were indistinguishable from each other. Two examples of these stimuli are provided in Figure 4-5.

Procedure. The Mental Rotation Task (MRT) was administered on the laptop computer, using the response button box to record the timing and accuracy of responses. The participant's task was to decide as quickly as possible whether the displayed stimulus represented a "left" hand or a "right" hand. The following instructions were read aloud by the examiner, while a written set of instructions was displayed on the computer screen: "*In this task, you will see a series of photos, one at a time. Decide whether it is a left hand or a right hand. If it is a left hand, then press this button with your left hand (examiner points to the left button). If it is a right hand, then press this button with your right hand (examiner points to the right button). Respond as quickly and as accurately as you can. Let's do a few trials for practice before trying the test, just so you get the hang of it.*"

Participants were administered 16 practice trials. They received feedback on a trial by trial basis regarding whether the response was correct. This was provided by the examiner and via a visual text box on the computer monitor. This practice section was used to ensure that the participants understood the task instructions. Following this



(A) (B)

Figure 4-5. Mental Rotation Task (MRT) example stimuli. (A) A “left” hand stimulus rotated 90 degrees inward from vertical (0 degrees), requiring a “left” hand button response. (B) Another “left” hand stimulus, rotated at 90 degrees outward, also requiring a “left” button response.

practice section, the examiner told the participant, "*Do you have any questions? Now you have the hang of it. You will now be presented with several sets of items, but you won't be told whether you are right or wrong. You will be provided with occasional breaks. Remember to respond as quickly and as accurately as you can*." Following these instructions, the test trials commenced. No feedback was provided concerning errors or correct responses during the test trials.

Each trial of the MRT began with a fixation mark, a crosshairs ("+"), that appeared for 500 ms in the center of the screen. This was immediately followed by a hand stimulus which remained on the screen until the subject responded. Participants were given as long as they wished to respond. There was an inter-trial interval of 2 seconds before the onset of a new fixation mark for the subsequent trial. A total of 64 test trials were administered and consisted of 4 blocks of 16 trials each with the primary stipulation of this order being that no stimulus orientation could be presented more than 3 times in succession. Each block consisted of a unique psuedorandomized order of the 16 photos in the stimulus set. After completing each block of stimuli, a message box appeared on the screen asking the participant whether a brief break was needed. Thus, opportunities for breaks were provided prior to the 17^{th}, 33^{rd}, and 49^{th} trials, with most participants choosing to continue the task within about 10 seconds. The total duration of this task was 10-15 minutes.

Data Reduction. Median response times (Ratcliffe, 1993) and error rates were obtained for each angle of rotation. Four angles of rotation were defined for the left and right hand stimuli: (1) <u>0-degrees</u> (upright), (2) <u>90-degrees rotated "inward"</u> (90-degrees rotated clockwise for the left hand, and 90-degrees rotated counterclockwise for the right hand), (3) 90-degrees rotated “outward” (90-degrees rotated counterclockwise for the left hand, and 90-degrees rotated clockwise for the right hand), and (4) 180 degrees (upside down). These conditions were abbreviated as “0”, “90-in”, “90-out”, and “180”, respectively[5]. The left and right hand stimuli, grouped by these four conditions, are depicted in Figure 4-6.

“Visual Search Task” (VST)

Rationale. The Visual Search Task (VST) was administered using the laptop computer with the button box to record responses. The task was adopted from the “hard feature serial visual search” task of Ellison, Schindler, Pattison, and Milner (2004). It requires participants to determine whether a particular, predefined target exists in a field of similar-looking, non-target items (using non-covert, free-ranging gaze). In their study of healthy adults, Ellison et al. found that the application of repetitive transcranial magnetic stimulation (rTMS) to the right superior temporal gyrus (rSTG) was associated with impaired performance on the VST (slower response times), but not on another task typically used in the diagnosis of neglect. Administration of rTMS to the right posterior parietal cortex (rPPC) showed the opposite pattern. Another research group (Gharabaghi, Berger, Tatagiba, & Karnath, 2006) supplemented these findings by demonstrating chance performance (51.3% correct) on this task in a patient during intraoperative, direct cortical stimulation of the middle portion of the rSTG (stimulation of this area did not affect performance on a simple feature visual search task or on a hard

[5] Pairing the left and right hand stimuli in this manner was done because the efficiency of mental rotating hand stimuli is influenced by biomechanical constraints; that is, it is difficult to mentally imagine and rotate images of hands that are physically difficult to generate with one’s own body (e.g., the dorsal view of one’s own upside-down hand) (Funk & Brugger, 2007). From this viewpoint, left and right hand stimuli are associated with different difficulty levels if they are paired by absolute angle of clockwise rotation, i.e., both hands rotated 90-degrees clockwise, or both hands rotated 90-degrees, counterclockwise. In contrast, left- and right-hand stimuli are similar in difficulty if “90-degrees rotated ‘in’” and “90-degrees rotated ‘out’” groupings are used.

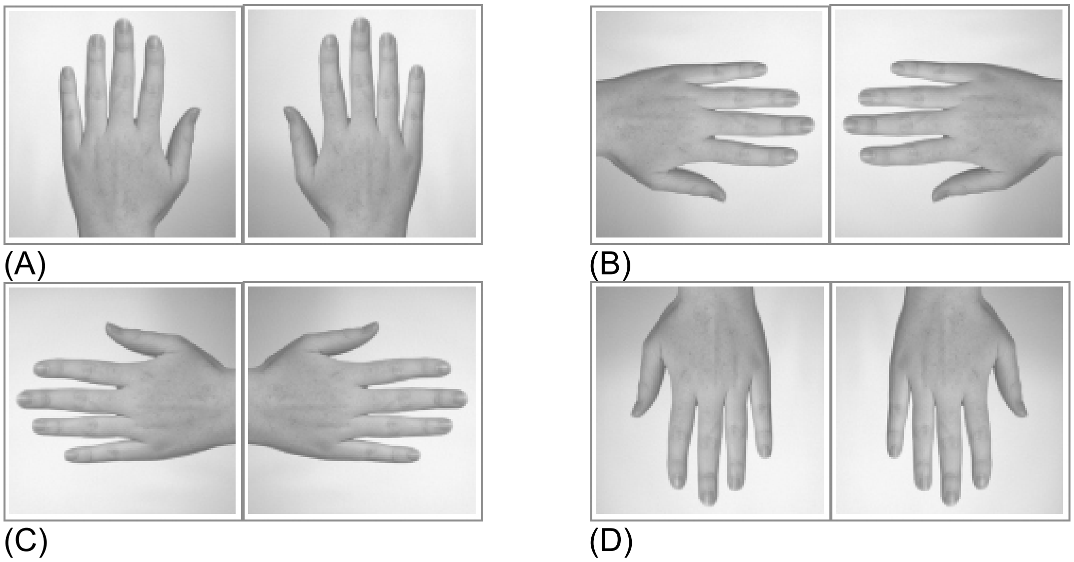
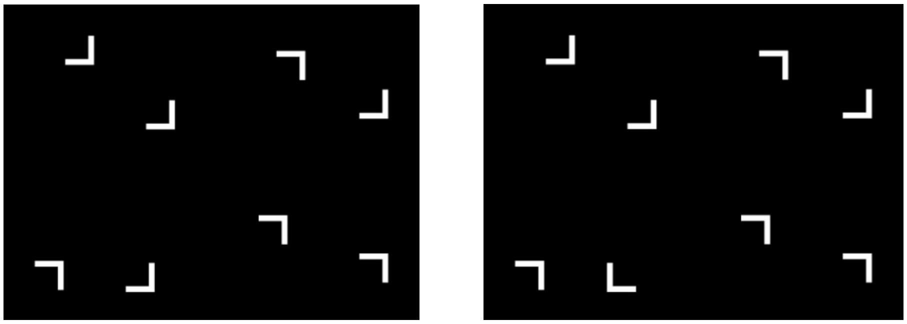


Figure 4-6. MRT example stimuli grouped by increasing degree of “biomechanical constraint.” Left and right hand stimuli are shown at the following angles of rotation: (A) 0 degrees, (B) 90 degrees “inward”, (C) 90 degrees “outward”, (D) 180 degrees (i.e., abbreviated 0, 90-in, 90-out, and 180). The female version of the hand stimulus set is shown.

conjunction search task). The patient had performed at 86.7% correct during an intraoperative baseline condition, and close to 100% performance prior to and after surgery. Direct stimulation of adjacent cortical areas, including the rPPC, demonstrated no significant reductions in performance. These two studies provide evidence that the rSTG is critical to hard-feature visual exploratory search and identification, at least, as measured by this task. The volumetrics study of ET by Daniels et al. (2006) found evidence of increased cortical density in right superior temporal gyrus (in patients with more longstanding ET). Thus, the visual search task of Ellison et al. (2004) was selected due to its potential for providing a sensitive means for detecting the presence of group differences, at least in this form of visuospatial processing (serial, hard-feature, exploratory visual search).

Stimuli. In the VST, participants indicated the presence of a unique target 'L' in a field of non-target items. The non-target items were identical to the target stimuli (i.e., shape, size, color), but differed in terms of orientations (rotated clockwise at 180 or 270 degrees). Eighty trials were created, each containing arrays of these items. Half of the trials contained one unique target 'L' with seven non-target items. The remaining 40 non-target trials contained eight non-target items. An equal number of each type of non-target item (180 or 270 degrees rotated 'L') was replaced by the target in non-target trials. In each trial, the eight items were distributed pseudorandomly and relatively evenly across the screen, with 2 items in each quadrant (upper left, upper right, lower left, lower right). Among the 40 target trials, the target appeared in each spatial quadrant an equal number of times (10), and its appearance in a given quadrant was balanced between the first and second halves of the test (5 each). Targets also appeared equally in the periphery (leftmost 25% of the screen, rightmost 25% of the screen) and the central area (middle 50% of the screen). Two stimulus orders were created and distributed across participants, with neither “non-target” nor “target” trials exceeding three in succession. Figure 4-7 shows example stimuli from the non-target and target conditions.

Procedure. This task was administered on the laptop computer and subjects responded manually using a button box. The following instructions were read aloud by the examiner, while a written set of instructions was displayed on the computer screen: “In this task, you are to look for a particular shape among a set of shapes spread across the screen. All the shapes will look similar, but this is the one you are looking for (examiner points to the target stimulus on the screen). If you see it on the screen, press this button with your right hand (examiner points to the right button). If not, press this button with your left hand (examiner points to the left button). Respond as quickly and as accurately as you can. Let’s do a few trials for practice before trying the test, just so you get the hang of it.” Participants were administered 10 practice trials, with visual (message box) and auditory feedback (examiner) as to whether each response was correct. This practice section was used to ensure that the participants understood the task instructions, and additional instructions were provided until the participants understood how to respond. Following this practice section, the examiner told the participant, “Do you have any questions? Now you have the hang of it. You will now be presented with several sets of items, but you won’t be told whether you are right or wrong. You will be provided with occasional breaks. Remember to respond as quickly and as accurately as you can.” Following these instructions, the test trials commenced.



(A) (B)

Figure 4-7. Visual Search Task (VST) example stimuli. (A) A ‘non-target’ stimulus array, requiring a “No/Left” button response. (B) Example of a stimulus array containing the target “L”, requiring a “Yes/Right” button response.

Across practice and test sections, each trial was preceded by a central fixation cross, “+”, that appeared for 500 ms, immediately followed by presentation of the stimulus array. Each stimulus array remained present until the participant pressed one or the other button, at which point the array disappeared for 2000 ms (black screen) prior to the appearance of the next fixation point. After every 20 trials, a message box appeared on the screen asking the participant whether a brief break was needed. Thus, opportunities for breaks were provided prior to the 21st, 41st, and 61st trials, with most participants choosing to continue the task within about 10 seconds. The total duration of this task was 10-15 minutes.

Data reduction. The two major dependent variables included response time (seconds) and error rates. These were derived from each of the two experimental conditions: a) trials on which a target was present and b) trials without a target stimulus. Median response times were derived from the correct trials (Ratcliffe, 1993). Error rates over all trials per condition were expressed as a value between 0 and 1. Thus, for each participant, four dependent variables were extracted: “Target RT”, “Non-target RT”, “Target Error Rate”, and “Non-target Error Rate”.

“Computer-Generated Arena” (C-G Arena) task

Overview. The Computer-Generated Arena (C-G Arena) task is a computer-based spatial navigation and memory task modeled after the Morris Water Maze, a paradigm classically used for studying spatial navigation and memory in rats (Jacobs, Laurance, & Thomas, 1997; Jacobs, Thomas, Laurance, & Nadel, 1998; Thomas, Hsu, Laurance, Nadel, & Jacobs, 2001; http://web.arizona.edu/~arg/). The participants viewed a computer monitor upon which they receive a first-person view of a virtual, 3-D room. A handheld, thumb-controlled direction pad is used to navigate within the room:

pressing up/down and left/right on the direction pad changes the first-person view on the monitor, such that these inputs simulate forward/backward movement, or spinning left/right. Navigation is constrained to a circular “arena” designed to look like a pool of water. The arena is bordered by a low wall and is in its entirety located in a perfectly square room, with each of the four walls of the room differentiated from the others by 1-2 unique, fractal-based patterns. Figure 4-8 depicts a schematic of the relative spatial arrangement of the room’s elements, as well as views of each of the walls.

Procedure. First, each participant was provided with up to 10 minutes of practice with the controller for navigation within a “practice room”. The room contained a visible white target and distinct, uniformly colored walls. The experimenter first modeled the use of the controller to move forward/backward (up/down on the control pad), spin left/right (rotation without translation; left/right on the control pad), and then combining directions using diagonal movements to move in arcs (i.e., translating forward/backward while spinning left/right: forward-left, forward-right, backward-left, backward-right). The participant then practiced these movements unaided until a general level of proficiency and ease of use was observed and reported. Following the practice session and demonstration of adequate mastery of the navigation controls, the test trials of C-G Arena commenced. Apart from this practice period (no participant took more than 5 minutes), the test trials of C-G Arena were divided into two sections/conditions, a “visible target trials” section and a “hidden target trials” section.

C-G Arena “visible target trials” (motor control task). This section of C-G Arena was designed as a motor control task, administered to provide measures of simple motor adeptness using the controls to navigate as intended. Additionally, it

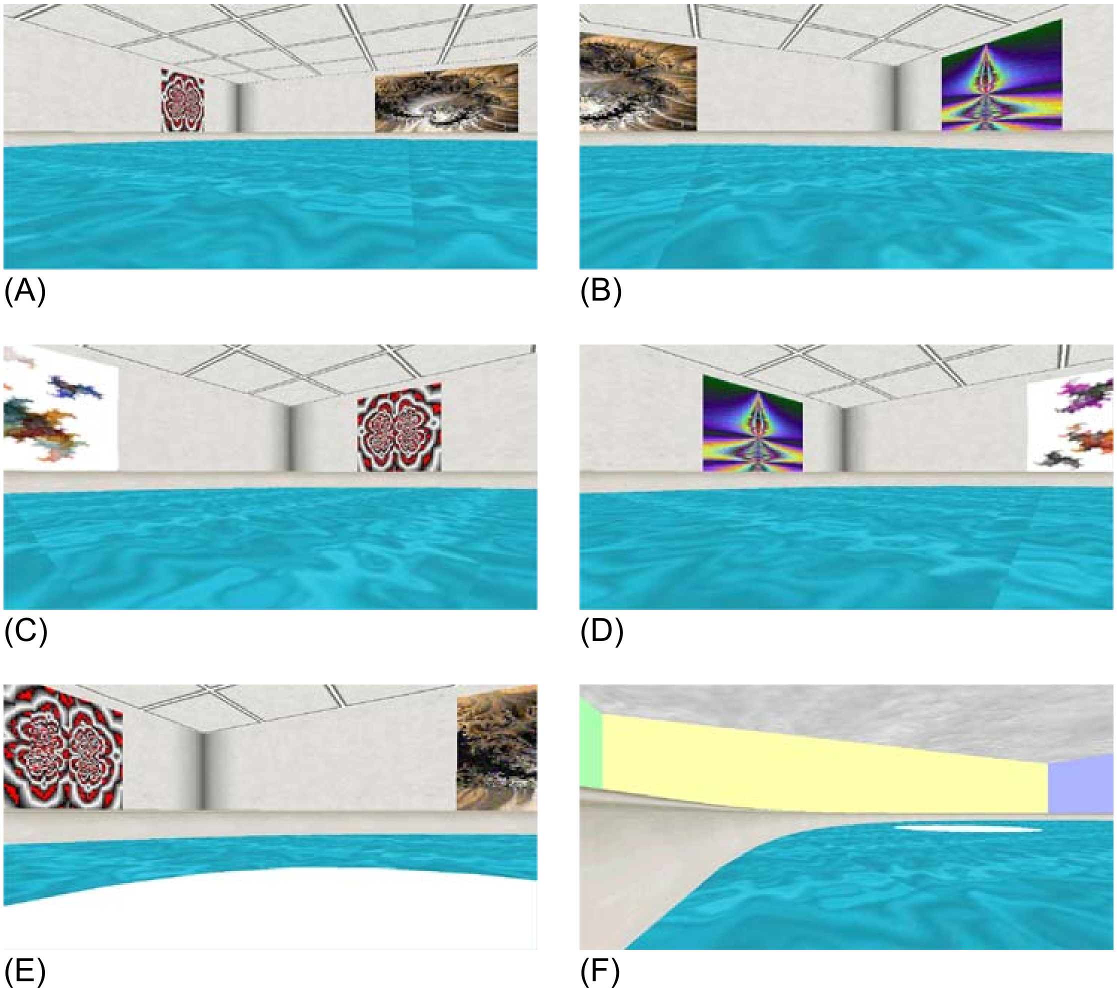


Figure 4-8. Computer-Generated Arena (C-G Arena) example views as seen by participants. Pictured from the “hidden target trials” (memory/learning condition) are the (A) northwest quadrant, (B) northeast quadrant, (C) southwest quadrant, and (D) southeast quadrant. (E) A view of the northwest quadrant containing the target, shown after target acquisition. (F) A view of the C-G Arena from the “visible targets trials” (motor control condition).

yielded data allowing analyses to rule out any motivational or perceptional problems when interacting with this virtual program. Group differences on the measures of this task would have implications upon the main C-G Arena spatial memory variables. For example, a potential group difference could be masked if ET patients possessed better spatial learning/memory for differences in basic motor control that would impact interpretation of results dependent the hidden target's location but, because of tremor, they had a more difficult time in using the controls in navigating as desired.

On this "visible target trials" section of C-G Arena, participants had to navigate within a room from different starting points and orientations (the initial direction faced) over 8 trials, with the objective of locating a visible, elliptical white target on the floor (also in different locations across trials) as quickly as possible. The target was within the field of view from the beginning of the first four trials, but on the last four trials, the participants had to turn substantially to bring the target within the field of view. The target was "located" when the participant successfully used the controls to navigate to the target and "stand" on top of it. Participants received immediate auditory feedback for a successful trial with presentation of a looped sound clip (i.e., "ta daa"). All participants received the same pseudorandomized order of start positions and target locations across the 8 trials (specified in Appendix B). Two dependent variables were extracted from this set of trials: (1) the length of the paths taken from starting positions to the visible targets (i.e., "total path length of visible trials"; summed over the 8 trials), and (2) the time taken from the onset of the trial to reach the targets (i.e., "total latency of visible trials"; also summed over the 8 trials). No participant demonstrated such poor control of the navigation device (due to tremor or other reasons) that testing could not proceed (subjective judgment by the experimenter).

C-G Arena "hidden target trials" (spatial navigation and memory). The main dependent measures of spatial navigation and memory were extracted from this section of the C-G Arena task ("hidden target trials"). Participants were required to find a hidden, spatially fixed target on the floor of a new room over 8 trials. All participants received the same pseudorandomized order of start positions and initial orientations across trials, as specified in Appendix B. First, they were provided a fixed "tour" of the new room, whereby the experimenter started from the south wall, oriented north, and navigated to the center of the room. The experimenter faced the north wall for 2 seconds before turning to the right to face the east wall. Turning clockwise in this manner, each wall was displayed for 2 seconds until the north wall was displayed again. The experimenter then turned counterclockwise and again faced each wall for 2 seconds before facing the north wall. During this "tour," the experimenter mentioned to each participant that a hidden target will be placed in a fixed location inside this room, and that they would have to search this room to find it as quickly as possible over each trial. Participants were informed that finding the target would be associated with visual feedback (the target appearing in white) and auditory feedback (presentation of the same looped "ta da" sound clip as was heard during the visible target trials. Finally, participants were told that failure to find the hidden target after 120 seconds in the first two trials would result in the experimenter taking over the controls at 120 seconds and finding the target for them (but that they should try their best to find the target on their own). Thus, target acquisition was guaranteed for all participants in the first 2 trials. No help or additional instructions were provided after the first 2 trials.

In this "hidden target trials" section of C-G Arena, spatial navigation and memory were assessed by (1) "total path length" over 8 trials to reach the target or the end of the trial (120 seconds), whichever occurred first, (2) "total latency" (seconds) over 8 trials between trial onset and reaching the target or the end of the trial, whichever occurred first, and (3) "total number of targets found" over 8 trials. After the 8^{th} trial, the hidden target was removed from its fixed location (covertly to the participant) in order to ensure that target acquisitions were not simply a result of trial and error. In this last (ninth) "probe" trial, spatial memory was assessed with the percent of time spent over the course of the trial in the correct quadrant of the room (i.e., where the target was located during the first 8 trials). The fourth measure of spatial learning and memory from the hidden targets trials, then, was (4) "percent time in target quadrant (probe trial)". This probe trial was important to ensure that participants were using the spatial cues to locate the target. If they were, they would spend the majority of the probe trial within the area of the arena where the platform was located during the initial eight trials.

Figure 4-8 shows depictions of this room used for the hidden targets trials, while Figure 4-9 shows a visual schematic to help illustrate how some of the dependent variables were calculated on the C-G Arena task. Appendix B provides the images used to texture the room's objects as well as the specific task parameters used in C-G Arena, for both the visible targets condition and the hidden targets condition.

"Object Attention Task" (OAT)

Overview. This experimental task provided a measure of object-based attention and was therefore used as a "control" task, as severe ET patients were expected to

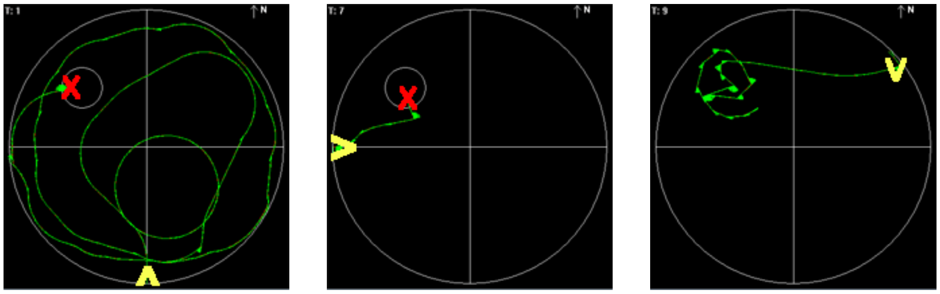

(A) (B) (C)

Figure 4-9. C-G Arena example path plots depicting spatial navigation and memory acquisition (“hidden target trials”). Plots depict the sample performance from a young female pilot participant, showing a bird’s eye schematic of the arena (available to the examiner only). Yellow arrows (which indicate start positions/orientations), green lines (which indicate paths taken), and red X’s (which indicate the end point of navigation) are shown, with the small white circle indicating the position of the hidden target. (A) Navigation is based on trial and error strategy for the first trial because the target is hidden and the location is not initially known. The target becomes visible when the participant passes over it. (B) Trial 7: after the fixed target location is found and learning occurs, subsequent trials such as this one are associated with more direct paths to the location of the hidden target (reflected by reduced path lengths and shorter latencies). (c) Probe (9th) trial: the target is removed, and participants who have learned the target location well spend most of the trial time searching the quadrant of the arena previously containing the target. This is reflected by a high percentage of the time spent during the probe trial in the “northwest” quadrant.

outperform mild ET patients only on spatially based tasks. This “object attention task” (OAT) was adapted from Behrman, Zemel, & Mozer (1998), who used this task in young, healthy adults to help provide evidence for a distinction between object and spatial attention strategies in visual perceptual processing. In their study, participants had to attend to and make simple judgments regarding two visual “features” apparent on overlapping rectangles. This task had two main conditions: (1) the two features were located on opposite ends of one of the rectangles (the one overlapping or overlapped by the other), or (2) on the two different rectangles. In the latter condition, the features in question are located closer together (see Figure 4-10 for examples of the stimuli). The use of a purely spatial attention strategy would predict faster reaction times for the simple judgments when the features were located on the two separate objects, because the features are closer together than in the single-object condition. Yet, the authors found the opposite effect: reaction times were faster when the features were located on opposite ends of the single object (spatially further apart), suggesting that object-based attention strategies are used in this task (for healthy and relatively young individuals).

Object-based attention phenomena such as this have been observed by others examining object-based, spatially invariant shifts of attention or maintenance of attention (e.g., O’Craven, Downing, Kanwisher, 1999; Yantis & Serences, 2003). These studies have lent further empirical support for object-based attention as a construct that is separate from spatial attention. They also partly have elucidated their neural networks using functional neuroimaging technologies such as fMRI.

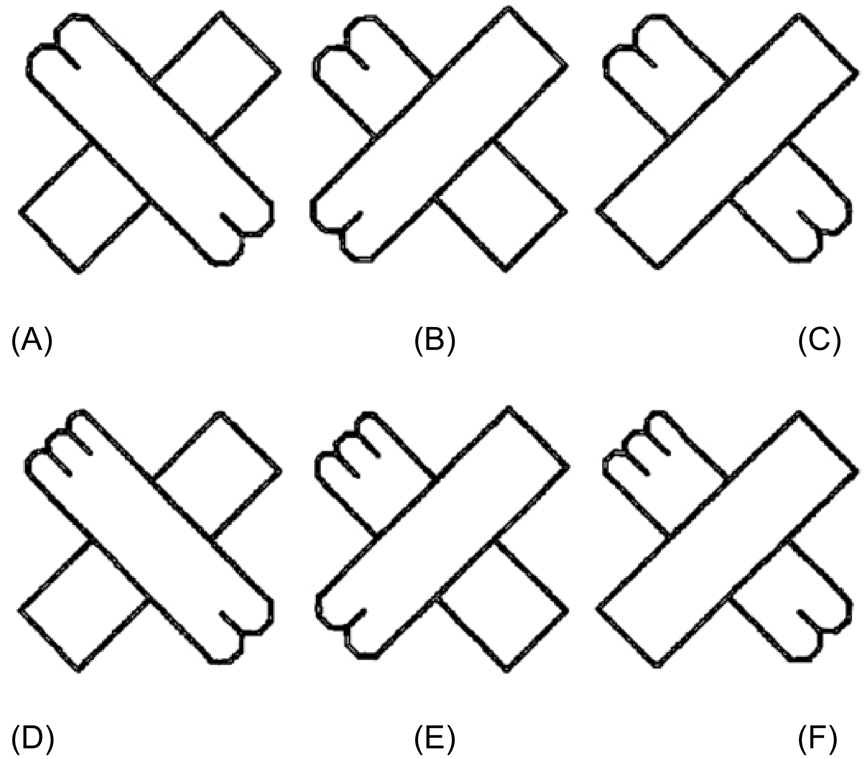


Figure 4-10. Object Attention Task (OAT) example stimuli. Top row: examples of stimuli requiring a “same object” judgment in the (A) one-object (unoccluded), (B) two-object, and (C) one-object (occluded) conditions, respectively. Bottom row: examples of stimuli requiring a “different object” judgment, in (D) one-object (unoccluded), (E) two-object, and (F) one-object (occluded) conditions, respectively. Use of primarily spatial attention would predict slower response times for same and different judgments in the one-object conditions, because in this condition, the features to be judged are spatially farther apart than in either of the one-object conditions (the distance is 41% greater). In healthy young adults, however, the fastest response times occur in the one-object conditions, suggesting that the normal response on this task utilizes object-based attention (Behrman et al., 1998).

Stimuli. As stated above, Figure 4-10 shows examples of the task stimuli. They were presented in black over a white background and were composed of two overlapping rectangles in an “X” pattern, with one rectangle overlapping the other. Two of the X-shaped figure’s four “arms” contained a set of features (“bumps”), made up of either two or three divisions at the edge. The number of bumps on each of the two arms was either the same (2-2 or 3-3), or different (2-3). These features appeared in two possible conditions: (1) at the ends of the same rectangle (the overlapping rectangle, or the rectangle that is overlapped by the other), (2) one feature on each of the two different overlapping rectangles (i.e., with the features spatially located at the bottom, top, left, or right pair of ends). The overlapping rectangles were oriented diagonally from top-left to bottom right, or diagonally bottom left to upper right in the figure. The entire stimulus set comprised every possible feature pairing and their spatial configurations, yielding 32 total stimuli. These stimuli and subcategories were constructed to match the specifications outlined by Behrman et al. (1998).

Task. The experimental procedure for this task also was modeled after the study by Behrman et al (1998). In each trial, a black fixation dot appeared centrally on the computer screen for 500 ms. This was followed by a delay of 1000 ms with a blank screen, and then a stimulus from the set. The participant was told to view the figure and decide, from the two edges of the figure containing bumps, whether the number of bumps on one edge was the <u>same</u> or <u>different</u> from the number of features on the other edge. Responses were indicated with the two available buttons on the response board, and each participant was told to respond as quickly and accurately as possible. Each response coincided with the stimulus disappearing from the screen for 1 second before the next trial.

The order of stimuli presented to each subject consisted of 4 blocks of pseudorandomized trials. These blocks were separated by brief pauses with durations as needed by the participants (typically less than 30 seconds). Each block consisted of 32 trials, half of which required “same” responses, and the other half required “different” responses. Among the 16 “same” trials, there were an equal number of 2-2 trials and 3-3 trials, and the locations of these features were counterbalanced in their spatial distribution (i.e., located on both rectangles in the figure, or the same). The spatial location of the features among the 16 “different” trials was also counterbalanced.
Prior to initiating the task, the administrator stated to each participant, “In this task, you will see a pair of rectangles that overlap to form an “X” with four arms. Here are some examples” (instructor points to example figures on the screen). “*You will notice that on two of the four arms, there are either one or two bumps on the end. Your task is to indicate if the number of bumps on one arm is the same or different from the number of bumps on the other arm. You would indicate “same” for this one (point) because the two arms with the bumps both have 2 bumps each. You would also say “same” for this one (point) because the two arms with the bumps both have 3 bumps each. So the number of bumps on each arm is the same, and so you would press this button (point). On the other hand, if the number of bumps on one arm does not match the number of bumps on the other arm, then you would press this button (point) to say that they are different in number. So for this one you would press “different”, and for this one, you would press “different”, because one arm has 2 bumps, and the other has three. Let's*

try a few practice trials so you get the hang of the directions. Respond as quickly and as accurately as you can." Following these instructions, participants were provided with 16 trials and visual and auditory feedback about errors following each one. The experimenter confirmed that the instructions were understood and answered any questions, and then the test trials commenced (no feedback about errors or correct responses). The total duration of this task was 10-15 minutes.

Data reduction. The raw data were reduced into response times over correct trials and error rates. These were grouped by the following conditions: "one object" (object attention) and "two objects" (spatial attention). Thus, the important point is that subjects were told to answer with "same" or "different" responses pertaining to whether the number of bumps matched; however, analyses distinguished only between whether the features that were judged were localized to one rectangle in the figure (one-object condition), or two different rectangles in the figure (two-objects condition).

Data Reduction & Analysis Plan for the Study

Reaction time (RT) variables were extracted from the relevant conditions of each of the timed computerized tests (Visual Search Test, Object Attention Test, Mental Rotations Test, and Choice Reaction Time Test) for each participant group (mild ET, severe ET, and controls). Each participant's RT data were calculated using the median RT value of all non-excluded (correct) trials (Ratcliffe, 1993) per condition and task.

Prior to each statistical analysis, all dependent variables were examined for normality, separately within each of the three subject groups. $Log_{10}(RT+1)$ transformations were applied to response time (RT) variables within a given analysis if Kolmogorov-Smirnov tests found any to be non-normally distributed ($p < .05$). Most experimental task error rates were also found to be non-normal using this criterion, and standard error rate transformations (arcsin, arcsin$\sqrt{x}$) were applied in these cases. Kolmogorov-Smirnov tests were re-performed after any transformations to re-check normality (*p*s > .05) before proceeding with parametric analyses. In cases whereby transformations insufficiently improved the normality of these distributions (Kolmogorov-Smirnov test *p*s < .05), non-parametric statistical procedures were performed. In all cases, *non*-transformed means and standard deviations are reported in the text, tables, and figures. The text specifies whether any transformations were applied prior to a given statistical analysis, as well as the type of analysis performed.

The primary analytic approach involved analyses of variance (ANOVAs) for Specific Aim 1 and hierarchical regressions for Specific Aim 2. <u>Specific aim 1</u> tested the hypothesis that severe ET has superior spatial cognition skills vs. mild ET, relative to controls. The associated analyses were designed to compare the three groups (severe ET, mild ET, control) in their performances on tasks of visual cognition, first for the spatial tasks (JOLO, MRT, VST, C-G Arena) and then for the object/form tasks (FRT, OAT). These analyses used ANOVAs or their non-parametric equivalents, and deconstructed main effects or interactions with post-hoc contrasts. Adjustments were made when appropriate in these analyses, e.g., the use of corrections for inflated familywise error rates (multiple tests) or adjustments to degrees of freedom due to violations of sphericity or variance assumptions.

<u>Specific aim 2</u> tested the hypothesis that ET severity (i.e., upper extremity tremor severity) is indeed a factor that contributes to spatial functioning, and not other potential explanatory variables such as education level, full-scale IQ, or age. Thus, it was predicted that tremor severity predicts a significant amount of variance in spatial

functioning, above and beyond other demographic, cognitive, or mood predictors. Only the 31 ET patients were used in these analyses. Spearman correlations were performed between spatial outcome variables (those that showed the "spatial superiority effect in severe ET") and potential predictors, which included upper extremity tremor severity, and demographic, cognitive (i.e., fronto-executive functioning measures), and mood variables. Variables correlating significantly with the spatial outcome measures were entered into separate linear regression analyses using a backward elimination procedure, with the purpose of identifying predictors that significantly account for each spatial outcome variable. Follow-up hierarchical regression analyses were performed using two models. Significant predictors were entered (forced entry) into the first model, unless predictors were theoretically or actually highly correlated. The second model held these predictors constant and tested the impact of upper extremity tremor score to determine whether the change in R^2 was significant, and whether the direction of the tremor severity predictor was as hypothesized in relation to the spatial score in question (positively). Collinearity, residual statistics, and leverage values also were examined for assumption testing and outliers in these models.

CHAPTER 5
RESULTS

Specific Aim 1: Group Comparisons on "Spatial" and "Object/Form" Measures

Overview

The first aim of this study was to test the hypothesis that individuals with severe upper extremity ET demonstrate superior spatial skills relative to those with mild upper extremity ET (see Figure 4-2). Spatial skills were measured by the Judgment of Line Orientation and three computerized experimental tests: the Visual Search Task (RT, error rate), Mental Rotations Task (RT, error rate), and the Computer-Generated Arena (number of hidden targets found, time to reach hidden targets, total path length to reach hidden targets, and percent time spent in the target quadrant during the final/probe trial). Group differences were also tested on visual "object/form" tasks (control tasks), wherein no group differences were expected to be found. These tasks included the Facial Recognition Test (a neuropsychological test) and the Object Attention Task (computerized experimental task). ET participants were not expected to outperform controls on either spatial or object/form visual tasks.

Demographic, Cognitive, and Mood Variables

Prior to testing these hypotheses, the two ET groups and the controls were compared on demographic variables, cognitive measures (those not in the spatial and object/form batteries), and self-reported mood scores. As was described in chapter 4 (Methods), non-significant one-way ANOVAs and chi-square tests found the mild ET, severe ET, and control groups to be comparable in age, education, gender ratio, handedness, and a full-scale IQ estimate. Additionally, in line with expectations, the severe ET group scored higher across tremor severity measures relative to the mild ET group. Table 4-2 provides these group characteristics.

Controls and the mild and severe ET groups then were compared on measures from the dementia screening tests, fronto-executive tests, and self-reported anxiety and mood (one-way ANOVAs with Bonferroni-corrected post-hoc comparisons, with an alpha criterion of .05). Means and standard deviations for these measures are provided in Table 5-1. The mild ET, severe ET, and control groups did not differ on anxiety (STAI-State, STAI-Trait), depression (BDI-II), or apathy (Apathy Scale) scores (ps > .5), but the severe ET group performed relatively poorly on several cognitive measures. Specifically, the severe ET group scored worse than controls on the Mini-Mental State Exam, the immediate and delayed recall portions of the WMS-III Logical Memory subtest, Digit Span, and the Stroop Color-Word interference condition, whereas the mild ET group performed comparably to controls on these measures. The severe ET group also scored worse relative to the mild ET group on the Boston Naming Test and Category Fluency, although neither ET group differed from the controls on these measures. Scores were within the unimpaired range (MMSE scores > 25; other scores > 5th percentile).

In sum, the three participant groups were comparable in demographic and mood variables, and the severe ET group scored higher across tremor severity measures relative to the mild ET group. The severe ET group tended to perform statistically worse on dementia screening measures and also demonstrated evidence of mild fronto-executive functioning deficits (<1 SD difference when compared with controls),

Table 5-1. Means (SD) by group for dementia screening, fronto-executive, and mood variables.

Dementia screening measure	*Control*	*ET mild*	*ET severe*
Mini-Mental State Exam	29.1 (0.9)	28.7 (1.0)	28.1 (1.5)*
WMS-III LM-I (SS)	12.9 (2.8)	12.8 (2.9)	10.5 (3.3)*
WMS-III LM-II (SS)	13.6 (2.8)	13.4 (2.6)	11.1 (2.6)*
Boston Naming Test (T-score)	53.3 (11.9)	58.9 (9.3)	48.6 (11.7)^
Fronto-Executive measures	*Control*	*ET mild*	*ET severe*
WMS-III Digit Span Total (SS)	11.9 (3.6)	11.4 (2.6)	9.3 (2.8)*
WMS-III Spatial Span (SS)	12.2 (2.8)	11.7 (1.6)	10.4 (4.3)
Stroop Color-Word (corrected raw score)	74.1 (11.3)	72.2 (10.9)	65.1 (12.2)*
Letter Fluency (FAS) (T-score)	48.1 (7.8)	47.8 (11.2)	42.6 (12.8)
Category Fluency (Animals) (T-score)	47.2 (9.4)	52.7 (7.6)	44.0 (10.6)^
Mood/anxiety measure	*Control*	*ET mild*	*ET severe*
STAI-State (T-score)	45.1 (7.9)	43.4 (9.1)	46.4 (8.5)
STAI-Trait (T-score)	47.1 (8.8)	45.1 (11.2)	49.5 (12.9)
BDI-2	5.4 (4.3)	6.2 (5.5)	6.8 (6.2)
Apathy Scale	9.5 (4.0)	10.6 (5.2)	10.8 (6.0)

Note: Values are expressed in means (SD). WMS-III = Wechsler Memory Scale, Third Edition; LM = Logical Memory; SS = scale score; TRS = Tremor Rating Scale; STAI = State-Trait Anxiety Scale; BDI-2 = Beck Depression Inventory, 2nd Edition.
* Severe ET group score < Control group score ($p < .05$).
^ Severe ET group score < Mild ET group score ($p < .05$).

consistent with the literature. All individual scores were within the unimpaired range due to the exclusion criteria that were applied.

CRT Results

Because some of the experimental measures are time-dependent, visuomotor reaction time (RT) of the left and right hands was recorded and compared among the ET groups and the controls. This was examined using a 3 (Group: control, mild ET, severe ET) x 2 (Hand: left, right) mixed-model ANOVA. The dependent variable was (normal) $\log_{10}$-transformed RT. Results of this ANOVA revealed a significant main effect of Group, $F(2,57) = 6.06$, $p < .01$, $\eta_p^2 = .175$. Bonferroni-adjusted pairwise comparisons revealed that RTs were slower for the severe ET group than for the mild ET group ($p < .05$, $r = .51$) and the control group ($p = .01$, r = .42). The severe ET group averaged about 0.1 seconds slower than the other two groups. No difference in RT was found between the mild ET participants and control participants ($p > .9$), nor were there significant Hand or Hand * Group interaction effects (*p*s > .3). Means and standard deviations for the RTs are provided in Table 5-2 and depicted in Figure 5-1.

Regarding error rates for the left hand and right hand (and the average error rate between the left and right hands), a group difference was found with a significant Kruskal-Wallis test for the right hand, $\chi^2(2) = 146.5$, $p < .01$. This was followed by Mann-Whitney paired comparisons, which found that controls made fewer errors with the right hand than the mild ET group (i.e., hitting the left button as opposed to the right button), $p < .01$. Surprisingly, the mild ET group also made more errors with the right hand than did the severe ET group, $p < .05$. No differences in error rates were found between the controls and the severe ET group (ps > .6) on the right hand. The three groups demonstrated similar error rates with the left hand as indicated by the non-

Table 5-2. Choice Reaction Time (CRT) task means (SD) by group

Measure	*Hand*	*Control*	*ET mild*	*ET severe*
CRT RT (seconds)	Left Hand	0.62 (0.11)	0.62 (0.08)	0.72 (0.13)*
	Right Hand	0.61 (0.12)	0.60 (0.08)	0.73 (0.14)*
CRT Error Rate	Left Hand	.013 (.034)	.020 (.056)	.023 (.044)
	Right Hand	.019 (.053)	.053 (.052)^	.008 (.028)

Note: "Motor speed" task. RT = Response Time (seconds). Error rate range: 0-1.
* RT: Severe ET group > (Control group, Mild ET group), p<.05
^ Error rate: Mild ET group > (Control group, Severe ET group), p<.05

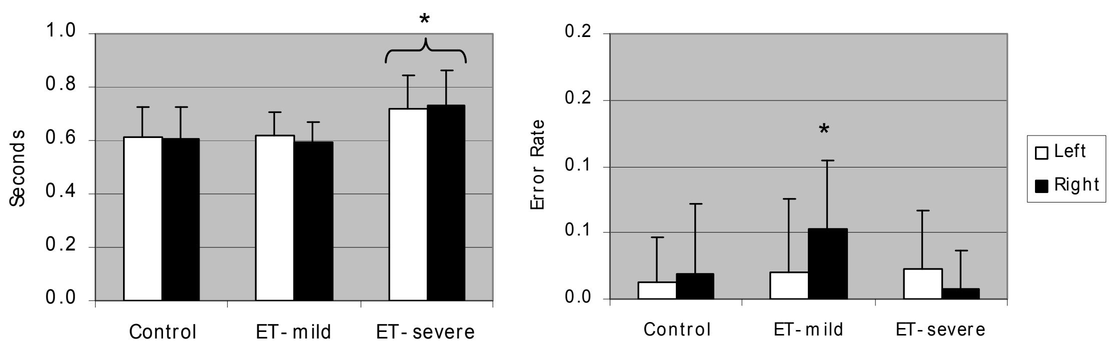


Figure 5-1. CRT performance by group, response hand. The severe ET group was slower than the control and mild ET groups. RTs did not vary by hand in any group. For error rates, the mild ET group committed more errors with the right hand than the other two groups.

significant Kruskal-Wallis test in this condition, $\chi^2(2) = .78$, $p = .68$. Means and standard deviations for the error rates are provided in Table 5-2 and depicted in Figure 5-1.

In sum, the CRT analyses found that the severe ET group was slower to respond than both the mild ET group and the controls, with the mild ET and control groups responding equally fast. The mild ET group made more errors of commission (right hand) than did the severe ET group or the controls.

Spatial Tasks (JOLO, MRT, VST, C-G Arena): Group Comparisons

JOLO results

Raw (and corrected) scores. Data derived from the JOLO were normally distributed for each subject group and variable (i.e., non-significant Kolmogorov-Smirnov tests, $p > .05$). Thus, a one-way ANOVA was performed to compare the raw JOLO scores among the mild ET, severe ET, and control groups. Results of the ANOVA revealed no significant group differences in raw JOLO scores, $F(2,62) = 1.56$, $p = .22$. This analysis was re-performed on JOLO scores corrected for gender and age (Benton, Sivan, Hamsher, Varney, and Spreen, 1994); however, this result also was not significant, $F(2,62) = 2.55$, $p > .05$. Means (SDs) are provided in Table 5-3 and depicted in Figure 5-2.

“High” vs. “low” performers. A secondary analysis was performed in order to replicate the approach taken by Springer et al. (2006). They found that a greater-than-expected proportion of older ET patients fell in the 51st to 100th percentile range on the JOLO (19 of 22 patients). This analysis was replicated in the present sample after combining the mild and severe ET groups. The ET participants’ raw JOLO scores were adjusted for age and education, converted into percentiles, and re-categorized as falling

Table 5-3. Judgment of Line Orientation (JOLO) means (SD) by group

Spatial measure	*Control*	*ET mild*	*ET severe*	*Test*
JOLO Raw score	24.0 (4.0)	22.9 (3.8)	21.7 (4.6)	*ns*
JOLO Corrected score (gender, age)	27.8 (3.9)	26.7 (3.6)	25.1 (4.1)	*ns*

Note: "Spatial" task.

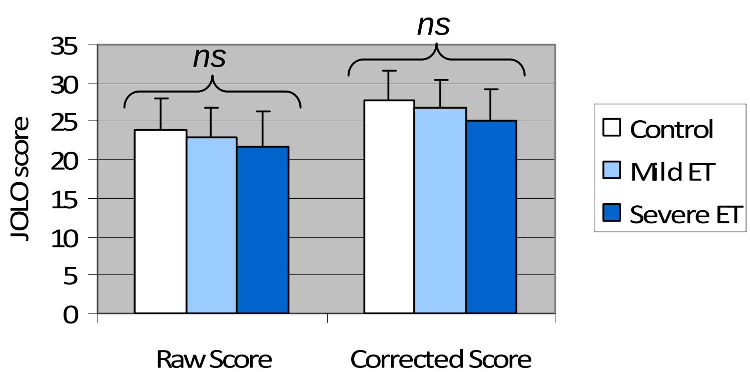


Figure 5-2. Judgment of Line Orientation raw scores and age- and gender-corrected scores. No group differences were found on either measure. Error bars represent standard deviations.

(a) above or (b) at/below the 50^{th} percentile. A chi-squared analysis was then performed to compare the actual number of participants with ET in each group with the expected proportion of ET participants in each group (i.e., n/2 in the upper-performing half and n/2 in the lower-performing half). Results were inconsistent with Springer et al. (2006). That is, the ET participants in the present study were not, as a group, disproportionately high scorers on the JOLO, $\chi^2(1) = 1.20$; $p = .27$, as only 18 of 30 ET patients scored in the 51^{st} to 100^{th} percentile range. In contrast, in the study by Springer et al. (2006), 19 of 22 severe ET patients fell in this better-performing category.

MRT results

Response times and error rates on the Mental Rotations Task were compared across four conditions for each group (mild ET, severe ET, control). As previously described (see Figure 4-7), the four main conditions represented hand stimuli rotated at 0, 90-in, 90-out, and 180 degrees. An initial analysis revealed no significant differences in error rates or RTs when left-hand responses and right-hand responses were compared; thus, these data were averaged at each angle of rotation. Error rates and RTs from the MRT are provided numerically (Table 5-4) and graphically (Figure 5-3).

MRT response times. First, the raw RT data were compared by group and angle of rotation. Non-significant Kolmogorov-Smirnov tests ($p > .05$) indicated that each of these variables was normally distributed, for controls as well as both ET groups. A 3x4 mixed-model ANOVA was performed, with a between-subjects factor of *Group* (mild ET, severe ET, control) and a within-subjects factor of *Angle* (rotated at 0, 90-in, 90-out, and 180 degrees). Mauchley's test was significant, $\chi^2(5) = 53.20$, $p < .001$, indicating that the assumption of sphericity was violated; therefore, Greenhouse-Geisser corrections were applied to the relevant degrees of freedom.

Table 5-4. Mental Rotation Test (MRT) means (SD) by group

Measure	*Angle of Rotation*	*Control*	*ET mild*	*ET severe*
MRT RT	0-degrees	1.29 (0.55)	1.30 (0.28)	2.08 (1.05)
	90-degrees/in	1.47 (0.45)	1.67 (0.39)	2.56 (1.68)
	90-degrees/out	1.74 (0.86)	2.31 (0.94)	3.11 (1.84)
	180-degrees	2.66 (1.06)	3.65 (1.40)	4.44 (2.26)
MRT Error Rate	0-degrees	3.98 (8.24)	5.86 (7.38)	3.66 (7.03)
	90-degrees/in	1.89 (3.31)	4.69 (12.40)	4.97 (5.11)
	90-degrees/out	4.55 (13.74)	6.25 (9.68)	6.04 (13.95)
	180-degrees	9.28 (12.51)	17.19 (18.33)	7.35 (12.18)

Note: "Spatial" task. RT = Response Time (seconds). See Figure 5-3 for significant differences.

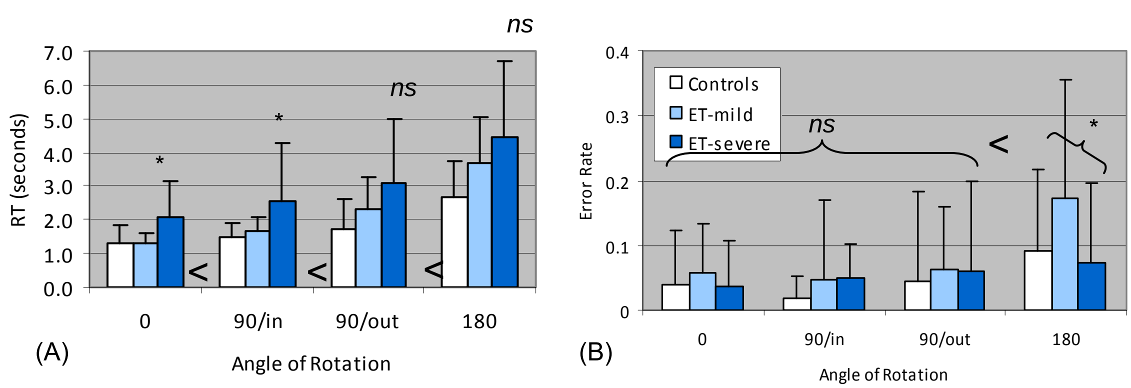


Figure 5-3. MRT performance by group (control, mild ET, severe ET), performance measure (RTs and error rates), and condition (angle of rotation). The severe ET group was slower than the mild ET group on the easiest conditions (0 and 90/in), but speed was significantly different in the harder conditions (90/out, 180). Although the 180 condition was associated with more errors than the other conditions, this pattern only held for the control and mild ET groups. In this condition, theoretically and empirically the most difficult, the severe ET group outperformed the mild ET group.

Results of the ANOVA revealed a significant effect of *Group* on RT, $F(2,58) = 9.40$, $p < .001$, $\eta_p^2 = .245$. In light of significant Levene's tests for the RT variables at all four angles of rotation (*p*s < .05), Games-Howell post-hoc procedures were used in deconstructing the significant *Group* effect. Post-hoc comparisons indicated no significant differences between the two ET groups ($p = .24$), though both were significantly slower to respond than the controls (*p*s < .05). The effect of *Angle* on RT also was significant, $F(1.83,106.29) = 95.21$, $p < .001$, $\eta_p^2 = .621$, as were all pairwise, post-hoc comparisons between angles of rotation (Bonferroni-adjusted, *p*s < .001); the fastest times were associated with the 0-degree condition, followed by 90-degrees rotated in, 90-degrees rotated out, and then 180 degrees / upside-down. This pattern was as expected, matching the order of conditions by increasing difficulty (i.e., greater effect of biomechanical constraint on visualizing the hand).

There was also a significant *Angle* * *Group* interaction $F(3.67,106.29) = 3.28$, $p < .05$, $\eta_p^2 = .102$. Post-hoc comparisons (Bonferroni-adjusted) showed that the severe ET group was slower than the controls and mild ET group in the two easier conditions (0 and 90-in). In the two more difficult conditions (90-out and 180), the severe ET group was comparable to the mild group (but slower than the controls; $p < .01$). The mild ET group did not differ in RT from the control group in any condition (*p*s > .05).

In sum, the severe ET group was slower than the mild ET group in the two easier mental rotation conditions (0, 90-in). However, the two ET groups were comparable in speed during the more difficult conditions (90-out, 180). The control group did not differ from the mild ET group in speed.

MRT error rates. Group error rates were compared using nonparametric analyses. First, separate Friedman's ANOVAs were performed to compare patterns of errors across the four angles of rotation for each participant group. The effect of Angle was significant for the control group, $\chi^2(3) = 12.66$, $p<.01$, and the mild ET group, $\chi^2(3) = 18.28$, $p < .001$; follow-up Wilcoxon rank-sum tests indicated that the 180-degree angle condition was associated with a significantly higher error rate than the other angles in these two groups (*p*s < .05). No differences were apparent among the other angles' error rates. While this pattern in errors (180 > [0 = 90-in = 90-out]) was found in the controls and participants with mild ET, it was *not* evident in the severe ET group: a Friedman's ANOVA showed that error rates did not vary by angle of rotation among severe ETs, $\chi^2(3) = 2.74$, $p = .43$). Mann-Whitney tests compared error rates among the three participant groups in the 180-degree condition alone, and found that the severe ET group made fewer errors than the mild ET group ($U = 65.00$, $p < .05$). No other group differences in error rates were found in the 180-degree condition. In sum, group-wise error rate analyses found that the 180-degree condition (the theoretically most difficult condition whereby the most mental rotation is required) was associated with relatively more errors than the others for both the control and mild ET groups, but not in the severe ET group. Moreover, the severe ET group outperformed the mild ET group in this condition, with significantly fewer errors.

MRT summary. Analysis of these data yielded several interesting findings. Regarding group differences in the speed of responses (RTs), the severe ET group was slower than the mild ET group in the two fastest conditions (0 and 90 degree inward), but this group difference disappeared in the two most difficult conditions (90-degree outward and 180 degrees). When error rates were compared across groups and conditions, it was found that the theoretically most difficult condition (180 degrees) was associated with the worst performance in the control group as expected, and this was also the case in the mild ET group. In the severe ET group, however, this pattern was not apparent, with error rates being similar across conditions. When the mild and severe ET groups were compared directly on the 180-degree condition, the severe ET group was found to outperform the mild ET group with significantly fewer errors (despite similar response times in this condition). This pattern was consistent with the hypothesis that spatial skills in severe ET are better than in mild ET, a pattern that emerged only in the most difficult condition of the Mental Rotations Test.

VST results

Next, performances on the Visual Search Task were compared by group (mild ET, severe ET, control) and condition (target trials, non-target trials). "Performance" was based on response times (RT) and error rates. RT and error rate means and standard deviations are transcribed in Table 5-5 and depicted in Figure 5-4, organized by group and condition (i.e., target vs. non-target trials).

VST response times. All VST variables were normally distributed after $\log_{10}$ (RT+1) transformations were applied. A 3x2 mixed-model ANOVA was performed with *Group* as the between-subjects factor and *Condition* (target trials, non-target trials) as the within-subjects factor. A significant *Condition* effect was found, $F(1,61) = 387.56$, $p < .001$, $\eta_p^2 = .864$, with faster responses being associated with target trials vs. non-target trials. The effect of *Group* on RT was significant as well, $F(2,61) = 3.49$, $p < .05$, $\eta_p^2 = .103$. Bonferroni-adjusted pos-hoc analyses demonstrated that the severe ET

Table 5-5. Visual Search Test (VST) means (SD) by group.

Task	*Condition*	*Control*	*ET mild*	*ET severe*
VST RT	Target trials	1.82 (0.37)	2.00 (0.43)	2.07 (0.64)
	Non-target trials	2.83 (0.60)	3.01 (0.60)	3.58 (1.08)
VST Error Rate	Target trials	10.30 (8.45)	6.41 (6.71)	12.00 (12.68)
	Non-target trials	1.14 (4.42)	0.78 (1.51)	3.17 (4.86)

Note: "Spatial" task. RT = Response Time (seconds). See Figure 5-4 for significant differences.

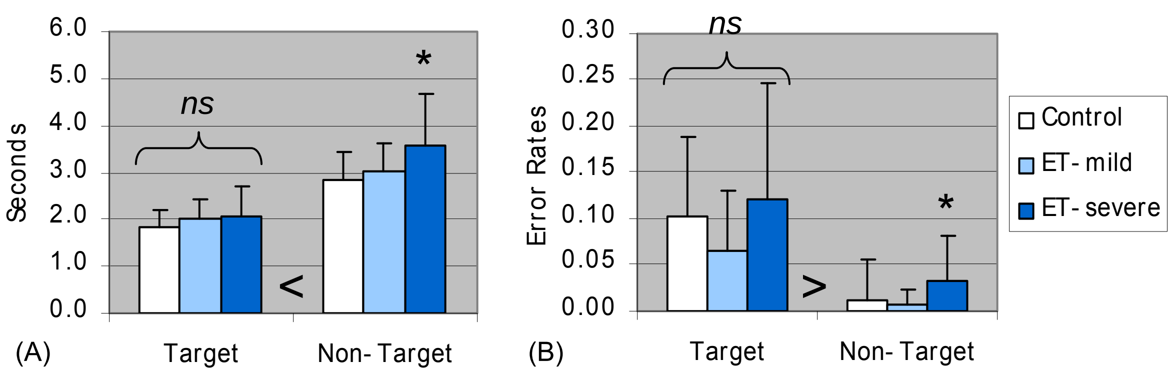


Figure 5-4. VST reaction times (A) and error rates (B), by group and condition. The severe ET group was slower and made more errors than the controls, but only in the non-target condition. Across groups, targets were recognized faster than non-target trials, although targets were missed (errors) more often than incorrectly recognized as being present. Error bars represent standard deviations.

group was slower than the control group, $p < .05$, while the mild ET group did not differ from either the controls or the severe ET group. These effects were qualified by a significant *Group*Condition* interaction, $F(2,61) = 3.37$, $p < .05$, $\eta_p^2 = .100$, which post-hoc comparisons indicated was due to group differences only during *non*-target trials. Specifically, the severe ET group was significantly slower than the controls in this condition, $p < .05$. There was also a tendency for the severe ET group to be slower than the mild ET group ($p = .09$). No difference was found between the controls and mild group on the non-target trials, and the three groups were comparably fast in the target condition (though a trend was found for the severe ET group to be slower than the controls, $p = .09$). No other comparisons were significant or reached trend level. *In summary, a comparison of response times by group on the visual search task revealed significantly slower RTs by the severe ET group relative to controls, but only during non-target trials of the Visual Search Task.*

VST error rates. Differences in error rates on the Visual Search Test then were tested between the control, mild ET, and severe ET groups. Non-parametric analyses were performed on these data because they were non-normally distributed despite attempts at normalizing them through transformations. First, three Wilcoxon signed-rank tests each compared errors in the target and non-target conditions, separately for each of the three participant groups. A Bonferroni correction was applied, and so all effects are reported at a .0167 level of significance. For all three groups, there were more errors in the target condition than the non-target condition (*p*s < .006). Kruskal-Wallis tests revealed that, similar to the RT analyses above, error rates differed between the three groups only during non-target trials, $\chi^2(2) = 6.28$, $p < .05$. Post-hoc

Mann-Whitney tests were performed for the non-target trial condition (also Bonferroni-corrected such that effects were reported at a .0167 level of significance) and revealed only that the severe ET group made more errors than the controls (U = 165.00, p = .016, r = -.35). Thus, the only significant group difference in error rates was that the severe ET group made more errors than the control group, and only in the non-target condition.

VST summary. Performance comparisons on the Visual Search Task found no group differences in speed or accuracy in finding the target shape on the screen. Group differences did emerge in the absent-target condition; that is, during non-target trials, the severe ET group was relatively slower and less accurate than controls in correctly ruling out the presence of the target shape. The mild ET group performed similarly to the severe ET group as well as controls (RTs, error rates), in both target and non-target conditions. That the severe ET group performed comparably to the mild ET group neither supported nor contradicted the spatial superiority hypothesis in severe ET. The finding that the severe ET group was slower and less accurate than controls during non-target trials may be a reflection of poorer spatial attention, worse visual discrimination between the similar-looking target and non-target shapes, or simply being more careful in ruling out the presence of a target (e.g., double checking each of the 8 shapes present on the screen). As a whole, participants behaved as expected on the task: participants were more likely to commit errors by missing targets that were present than to mistakenly indicate their presence. Regarding speed, participants were quicker to identify a target than to indicate its absence (correct trials).

C-G Arena results

Motor control ("visible target" trials). Before comparing group performances in spatial memory/navigation on the C-G Arena task, it was necessary to test for differences in basic motor control of the thumb-operated control pad (differences in basic motor control on this task would affect interpretation of results involving the spatial memory variables). Two variables were extracted from these visible target trials: total path length taken ("Arena units") and total latency (seconds) to reach the visible targets. As neither variable was normally distributed, Kruskal-Wallis tests were conducted to determine whether performances varied by group (severe ET, mild ET, controls). Neither test was significant (*p*s > .5); thus, the three groups demonstrated equal proficiency in visuomotor control as measured by this subtask. Figure 5-5 below depicts these results graphically; means and standard deviations are provided in Table 5-6. As a follow-up to these analyses, Spearman correlations were performed between upper extremity tremor severity and the total latency and path length variables from the visible-target trials (among all ET participants). None of these correlations were significant (*p*s > .1), suggesting that tremor severity did not impact basic use of the controls on the C-G Arena task. These results also were suggestive of similar levels of motivation and task-specific perceptual ability for the "3-D" virtual environment.

Spatial memory ("hidden target" trials). From the eight "Hidden Target" trials portion of the C-G Arena task, four variables were extracted from the participants' performances: (1) total path length across trials (measured in C-G Arena units), (2) total latency across trials (in seconds), (3) number of targets acquired (range: 0-8), and (4) percentage of time in the target quadrant during the ninth, probe trial (after removal of the hidden target). Non-significant Kolmogorov-Smirnov tests found that all four of

Table 5-6. C-G Arena means (SD) by group.

Condition	*Measure*	*Control*	*ET mild*	*ET severe*
Visible Targets	Total latency	51.2 (9.9)	52.4 (12.3)	53.9 (10.2)
	Total path length	545.2 (58.8)	540.8 (27.9)	534.4 (23.4)
Hidden Targets	Total latency	301.8 (117.0)	254.1 (122.4)	297.4 (113.0)
	Total path length	2,390 (1,049)	1,924 (782)	2,298 (1,160)
	Total targets found	6.3 (1.6)	5.3 (2.1)	6.1 (1.2)
	% time in quadrant*	38.1 (23.5)	22.6 (25.6)	45.4 (24.9)

Note: "Spatial" task. "Hidden Target Trials" refers to the "Spatial Navigation/Memory" portion of C-G Arena, and "Visible Target Trials" refers to the motor control task portion of C-G Arena. Significant differences are described in the text and in Figure 5-6.
*Target quadrant, probe trial.

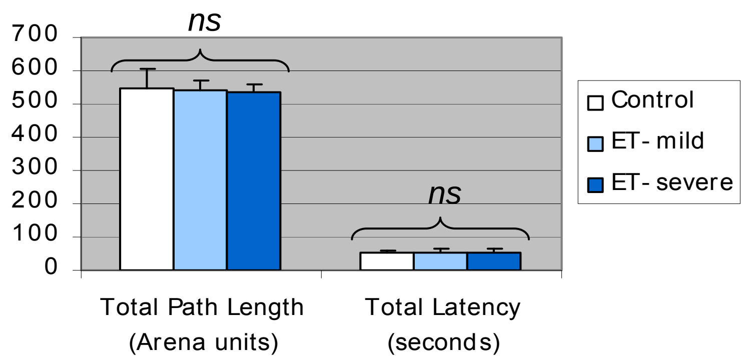


Figure 5-5. Motor control on C-G Arena (“visible targets trials”). Analyses revealed no group differences in total path length or total latency to reach the eight visible targets, indicating that the three groups could use the controls at a similar level of efficiency.

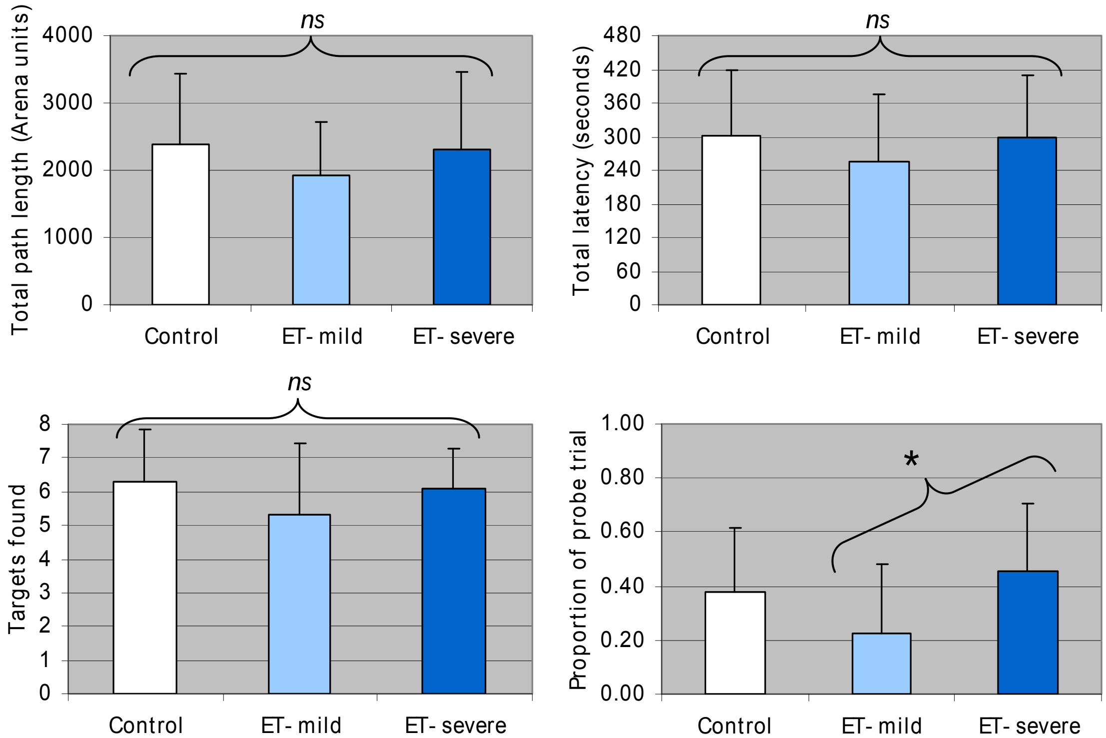


Figure 5-6 C-G Arena "hidden target trials" performance by group: (A) total path length, (B) total latency, (C) targets found, (D) percentage of time (in the target quadrant during the probe trial). Group differences were found only in Figure D (severe ET > mild ET on this measure of spatial memory for the target location). For (A) and (B), higher numbers are associated with *worse* performance, but for (C) and (D), higher numbers are associated with *better* performance.

these variables were normally distributed for the mild ET, severe ET, and control groups. Table 5-6 provides the means and standard deviations for these measures. One-Way ANOVAs were performed on each variable, using *Group* as the between-subjects factor. As shown in Figure 5-6, the only significant group difference was found for the dependent variable, “time in the target quadrant” during the probe trial, $F(2,62) = 3.59$, $p < .05$, $\omega^2 = .076$. Bonferroni-corrected pairwise comparisons indicated that the severe ET group scored better than the mild ET group on this measure (i.e., a higher proportion of time spent in the target quadrant). No other group comparisons were significant on this measure. *In sum, there was some limited evidence consistent with the hypothesis that more severe tremor is associated with better spatial functioning; on the C-G Arena task, the severe ET group outperformed the mild ET group on a measure of spatial memory, although no other group differences were indicated from any of the analyses.*

Object/Form Tasks (FRT, OAT): Group Comparisons

FRT results

Raw (and corrected) scores. *A* one-way ANOVA was conducted to test for group differences in raw scores on the short-form FRT among the mild ET, severe ET, and control groups. Distributions by group were normal according to Komogorov-Smirnov testing (ps > .05). No significant effect of group was found on the raw FRT scores, $F(2,62) = 1.68$, $p > .05$, nor was this analysis significant when it was re-performed on age- and education-corrected long-form FRT scores, $F(2,61) = 1.57$, $p > .05$. Means and standard deviations are provided in Table 5-7 and depicted graphically in Figure 5-7.

Table 5-7. Facial Recognition Test (FRT) means (SD) by group.

Measure	*Control*	*ET mild*	*ET severe*
Raw score (short form)	21.5 (2.4)	22.4 (2.2)	20.9 (2.4)
Corrected score (education, age)	45.7 (4.5)	47.4 (4.1)	44.5 (4.9)

Note: Object/Form Task. No significant group differences on this test as predicted.

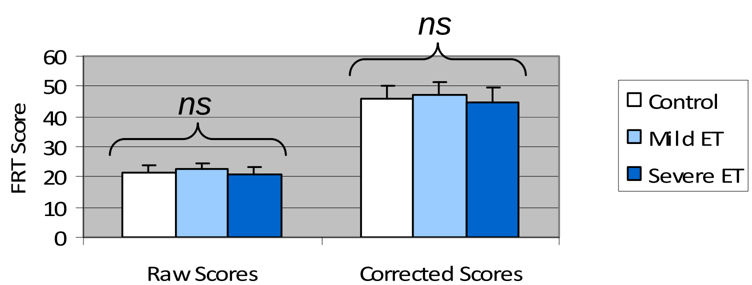


Figure 5-7. Facial Recognition Test raw scores (short form) and age- and education-corrected scores (after long-form conversion). No group differences were found on either measure. Error bars represent standard deviations.

OAT results

Group differences were tested on four dependent variables extracted from the Object Attention Task. These variables were RTs and error rates when judging two object-based features in two conditions: (1) the "one-object" condition, in which the two feature judgments were made on a single object, and (2) the "two-object" condition, in which the two feature judgments occurred on two different (overlapping) objects but were spatially closer. The raw RT variables were not normally distributed for most groups and conditions, but normality for all RT variables was confirmed with Kolmogorov-Smirnov tests ($p > .05$) after applying log transformations. Error rates remained non-normal after transformation, and so non-parametric statistics were performed on these data. RT and error rate values extracted from the OAT are provided by group in Table 5-8, and displayed graphically in Figure 5-8.

OAT response times. A 3x2 mixed-model ANOVA was performed to test group differences in the two conditions. *Group* (mild ET, severe ET, control) was the between-subjects factor, and *Condition* (one object, two objects) was the within-subjects factor. The main effect of *Condition* was significant, $F(1,60) = 18.43$, $p < .001$, such that RTs were faster for the one-object condition than they were for the two-object condition. The effect of *Group* on RT also was significant, $F(2,60) = 5.08$, $p < .01$, $\eta_p^2 = .235$, and Bonferroni-corrected post-hoc analyses indicated that the severe ET group was slower than the control group overall, $p < .01$). No other group differences were significant. The *Group* * *Condition* interaction also was not significant ($p > .4$). *In sum, RT analyses on the OAT found that the severe ET patients were slower than the other groups in making correct feature judgments. The mild ET group did not differ in RT from controls or the ET group with more severe tremor.*

OAT error rates. The severe ET, mild ET, and control groups also were compared for differences in error rates over the one-object and two-object conditions. Bonferroni-corrected Wilcoxon tests, evaluated at a significance level of .0167, compared error rates in these conditions among the three groups. Error rates did not differ significantly between the one- and two-object conditions for any group (ps > .08). Two Kruskal-Wallis tests found that error rates in both the one-object and two-object conditions did not differ between the three groups (ps > .2). Thus, error rates did not vary by group or condition on the OAT.

OAT results summary. Results of the above analyses showed that error rates did not vary by group or condition, and relative to controls, the severe ET group had longer response times regardless of the condition (i.e., whether the perceptual judgments were made on one or two objects). The severe ET group did not differ from the mild ET group in RT. Taken together, these results are consistent with the initial hypothesis that severe and mild ET would not differ on this “object/form” task, as the two groups, divided by tremor severity, were hypothesized to differ only on spatial tasks. The difference in RT between controls and the severe group was similar in direction and magnitude to that found on the CRT and therefore appears to reflect merely a group difference in motor RT rather than a substantial difference in object-based attention.

The finding that perceptual judgments in the two-object condition were slower than those in the one-object condition is consistent with findings in young adults by Behrman and colleagues (1998), the original authors of this task. Similar to the present results, Behrman and colleagues found faster RTs for perceptual judgments when the features to be judged occurred on one object. This was established in their study as well as the

Table 5-8. Object Attention Test (OAT) means (SD) by group.

Task	*Condition*	*Control*	*ET mild*	*ET severe*
OAT RT*	1-Object trials	1.05 (0.18)	1.12 (0.21)	1.28 (0.33)
	2-Objects trials	1.07 (0.20)	1.14 (0.21)	1.32 (0.35)
OAT Error Rate	1-Object trials	1.12 (2.22)	2.15 (4.03)	2.19 (2.94)
	2-Objects trials	0.93 (0.96)	1.76 (4.63)	0.83 (1.43)

Note: "Object/Form" test. RT = Response Time (seconds).
*The severe ET group was slower than Control group on this task overall (*p*<.01), and the 2-Objects condition was associated with slower RTs than the 1-Object condition (*p*<.001). No group differences between Severe ET and Mild ET groups, as predicted.

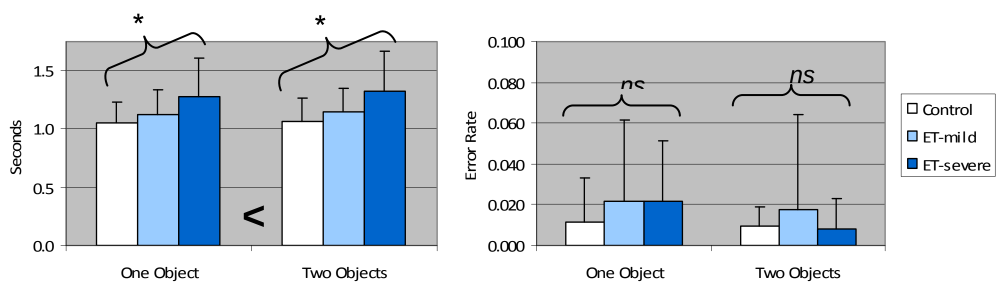


Figure 5-8. OAT reaction times and error rates by group. The severe ET group was, overall, slower than the control group on this test, and the severe ET and mild ET groups were statistically equal in speed. No group differences were found in error rates.

present one, despite the fact that the two features to be judged always were located substantially further apart in the one-object condition relative to the two-object condition (approximately 41% further apart; see Figure 4-10). The present findings support object-based attention in older adults, with or without ET.

Summary of Specific Aim Results: Group Comparisons on Spatial vs. Object/Form Tasks

This set of analyses compared performances on visual "spatial" vs. "object/form" measures for groups of individuals with either mild, severe, or no ET (controls), with mild vs. severe ET group membership defined by the severity (i.e., amplitude) of upper extremity postural/kinetic tremor. Based on previous findings, it was hypothesized that the severe ET group would outperform the mild ET group on spatially loaded tasks, but not on object/form perception tasks.

On the whole, results from these analyses were partially consistent with this hypothesis. The severe ET group outperformed the mild ET group on two of the four spatial tasks. Specifically, the severe ET group made fewer errors than the mild ET group on the most difficult condition of the Mental Rotations Task (180-degrees of rotation), and they also demonstrated better spatial memory on the computer-generated Arena task (i.e., spending more time searching the correct area for the target following the learning trials (1-8). On the other two spatial tasks, the mild ET and severe ET groups performed similarly. That is, the two groups identified the presence of a target shape with similar accuracy and speed on the Visual Search Task, and they also demonstrated similar perceptual ability in identifying the angular orientations of lines relative to items in a reference array. There was no evidence to suggest that the mild ET group outperformed the severe ET group on any spatial measure. Relative to the controls, neither ET group showed greater accuracy or speed on any of the spatial tests.

On the two visual object/form perception tasks, the severe and mild ET groups performed comparably, as hypothesized. They demonstrated equal ability in the recognition and discrimination of unfamiliar faces portrayed under normal and unusual lighting conditions. They also performed comparably (accuracy and RT) on a task requiring efficient perceptual judgments of overlapping figures. As was the case on the spatial tasks, neither of the two ET groups outperformed controls at a statistically significant level on either of these object/form tasks.

Analysis of demographic and cognitive measures demonstrated that the severe ET group and the mild ET group were statistically comparable to each other and controls in age, gender ratio, education, handedness, a full-scale IQ estimate, and mood/anxiety scores. While no member of either ET group was impaired on dementia screening measures (MMSE, Logical Memory subtest of the WMS-III, Boston Naming Test), the severe ET group as a whole scored statistically worse on the MMSE, Logical Memory immediate and delayed recall, and Boston Naming. Finally, the severe ET group was slower than the mild ET group and controls on a measure of simple visuomotor response time using the button box (about 0.1 seconds on average). As a whole, these "impairments" in the severe ET group were relatively small, but they nevertheless reduce the likelihood that the evidence for *better* spatial performances of the severe ET group vs. the mild ET group on two of four spatial tests was due to group differences in some other factor.

Specific Aim 2: Controlling for Other Variables in the Spatial Superiority in Severe ET Effect Using Hierarchical Regressions

Overview

The second aim of this study was to rule out other potential factors underlying the spatial superiority effect in severe ET (mental rotations, spatial memory/navigation). Analyses in the first specific aim already established that the mild ET and severe ET groups were statistically similar across demographic and mood variables, and the severe ET group scored *worse* on several cognitive measures (albeit mildly so) and motor speed on the Choice Reaction Time task. Aside from upper extremity tremor severity, then, no other causal factor for the superior spatial effect in the severe ET group is immediately obvious. The paradoxical relationship between higher tremor severity and better spatial skills has not been described previously in the literature, however; thus, the burden of proof is greater.

For this reason, the next set of analyses was designed to test more rigorously whether upper extremity tremor severity significantly and positively predicts spatial functioning in ET above and beyond other predictor variables such as sociodemographic characteristics, fronto-executive measures, or mood measures. To achieve this end, two hierarchical regression analyses were planned, one for each of the two spatial outcome measures whereby the spatial superiority effect in severe ET was demonstrated: (1) the Mental Rotations Task error rate in the 180 degrees condition and (2) the Arena proportion of time spent searching the target quadrant during the probe trial. The controls were not included in these analyses, and both the mild and severe ET groups were combined into one sample.

Analyses

To begin, the MRT and Arena outcome variables were correlated with upper extremity tremor severity and demographic, cognitive (fronto-executive), and mood variables, in order to determine basic associations with spatial functioning. The zero-order Spearman correlation coefficients are presented in Table 5-9 and characterize relationships between each spatial outcome variable and the potential predictor variables. The set of potential predictor variables included upper extremity tremor severity, demographic variables (gender [recoded: 1 = male, 2 = female], age, education, full-scale IQ estimate), fronto-executive measures (Digit Span total, Spatial Span total, Stroop Color-Word[CW], Letter Fluency, Category Fluency) and self-reported mood measures (STAI-State, STAI-Trait, BDI-2, and Apathy Scale).

As shown in Table 5-9, <u>MRT error rate</u> (180-degrees) was negatively correlated with tremor severity (i.e., fewer MRT errors / higher accuracy was associated with *more* severe tremor as predicted). It was also positively correlated (i.e., associated with worse performance) with female gender, age, and category fluency (ps $< .05$). A negative correlation with Stroop CW (interference) was borderline significant ($p = .05$). <u>Arena % time</u> was positively correlated with tremor severity (i.e., better spatial memory / navigation associated with *more* severe tremor), and negatively correlated (i.e., associated with better spatial memory) with female gender, age, and STAI (state and trait) scores. Finally, correlations were examined between tremor severity and these (non-spatial) variables that correlated significantly with either of the two spatial scores. <u>Tremor severity</u> was only significantly associated (inversely) with category fluency (r = -.35, $p > .05$). Tremor severity tended to correlate with male gender ($p > .07$), but this did not reach significance.

Table 5-9. Correlations with “Spatial Superiority” Variables in ET

Domain	*Predictor*	*Correlation with MRT 180 Errors*[1]	*Correlation with Arena % Time*[2]
Disease Severity	Upper Extremity Tremor	-.32*	.45**
Demographic	Gender (1=male, 2=female)	.41*	-.45**
	Age	.33*	-.43**
	Education	.17	.00
	FSIQ estimate	.08	.04
Fronto-Executive	Digit Span total	.03	-.02
	Spatial Span total	-.19	-.01
	Stroop CW (interference)	-.31^	-.10
	Letter Fluency	.10	-.03
	Category Fluency	.29*	-.14
Mood/Anxiety	STAI-State	.13	-.40*
	STAI-Trait	.05	-.33*
	BDI-2	-.01	-.06
	Apathy Scale	.11	-.05

1 MRT-180 Errors = Mental Rotations Test, 180-degrees Condition (Error Rate)
2 Arena % Time = Percent of time spent on probe trial in target quadrant
**p<.01, *p<.05, ^p=.05

After these analyses were performed, the significant correlates for each of the two spatial measures were entered into separate exploratory linear regression analyses using a backward elimination procedure (one analysis using MRT error rate at 180 degrees as the outcome variable, and the other using Arena percent of probe time in the target quadrant as the outcome variable). These analyses determined which of these predictors for each spatial variable remained significantly predictive of spatial functioning when considered together. Follow-up hierarchical linear regression analyses tested the independent contribution of upper extremity tremor severity to spatial cognition (MRT or Arena performance), above and beyond the predictor variables identified by the exploratory regression analyses. Below, the analyses for the MRT outcome variable are presented first, followed by those for the Arena outcome variable.

MRT (180-degrees condition) regressions

Regressing upper extremity tremor severity, gender, age, category fluency, and Stroop CW scores on MRT error rate with the backwards elimination procedure found the final significant model, $R^2 = 0.240$, $F(2,27) = 3.96$, $p < .05$, with two variables as the only significant predictors of MRT error rate at 180 degrees. These were upper extremity tremor severity, $\beta = -.37$, $t(27) = -2.10$, $p < .05$, and Stroop Color-Word, $\beta = -.37$, $t(27) = -2.11$, $p < .05$.

Subsequently, these two predictors were regressed upon MRT performance in a hierarchical regression analysis yielding two models. Results are provided in Table 5-10. In the first model, the effect of Stroop CW upon MRT errors alone was described. Significance for this model reached trend level, $R^2 = .11$, $F(1,26) = 3.11$, $p = .09$, with Stroop CW $\beta = -.33$. In the second model, in which MRT errors were regressed upon both Stroop CW and upper extremity tremor severity, 13% additional variance was accounted for, attributable entirely to upper extremity tremor severity, R^2-change = .134, F-change(1,25) = 4.40, $p < .05$. The overall model was significant, $R^2 = 0.240$, $F(2,27) = 3.96$, $p < .05$, as were the coefficients for each predictor variable, Stroop CW $\beta = -.37$, upper extremity tremor $\beta = -.37$, ps < .05. These results indicate that more severe upper extremity tremor significantly predicted *fewer* errors on the most difficult condition of the mental rotations task, above and beyond the enhancing effect of cognitive inhibition (as measured by Stroop CW measure) on these kinds of mental operations.

Tolerance and VIF values were examined for evidence of collinearity, for each of these predictor variables. Both sets of values were found to be acceptable, with VIF values = 1.01, and tolerance values greater than .2 (i.e., both .99). None of the residuals in this analysis fell outside a 3-SD range, and all leverage values were acceptable at less than .5 (max value = .33). For these reasons, the model was considered robust and not influenced unduly by outlying data points.

C-G Arena percent time (probe) regressions

Upper extremity tremor severity, gender (male = 1, female = 2), age, and STAI-State were regressed upon Arena % Quadrant Time using the backwards elimination procedure to determine which variables remained predictive of spatial memory when considered together. STAI-Trait was not included in this analysis because it correlated highly with STAI-Trait scores ($r = .77$, $p < .01$) and was considered to be less theoretically relevant to Arena performance (i.e., STAI-State is a measure more closely related to anxiety during task performance, as it measures anxiety in the moment of filling out the questionnaire). This analysis mathematically eliminated gender as a predictor to form a significant model, $R^2 = 0.482$, $F(3,27) = 7.45$, $p < .01$, with the remaining predictors being significant: age, β = -.56, $t(27) = -3.45$, $p < .01$; STAI-State, β = -.56, $t(27) = -3.47$, $p < .01$; and upper extremity tremor severity, β = .39, $t(27) = 2.66$, $p < .05$.

Age, STAI-State, and upper extremity tremor were then used as predictors in a hierarchical regression with the Arena % time being the outcome variable. Age and state anxiety were entered in an initial model and tremor severity in the second to test its independent contribution to the spatial score. Results of this analysis are provided in Table 5-10. The first model was significant and accounted for 33% of the variance in spatial memory on the Arena task, $R^2 = .330$, $F(2,27) = 6.16$, $p < .01$. Both predictors (age and situational anxiety) were significant in this model (*p*s < .01). The second model was also significant, $R^2 = .482$, $F(3,27) = 7.45$, $p = .001$, and tremor severity was found to make a significant independent contribution to spatial memory on this Arena task (15% of the variance), above and beyond age and STAI anxiety/arousal, R^2-change = .152, F-change(1,2247) = 7.06, $p < .05$. All three coefficients were significant, with Age β = -.56, STAI-State β = -.56, UE Tremor β = .39; *p*s < .05. Thus, greater upper extremity tremor predicted significantly better spatial memory performance on the Arena task, above and beyond age (older age being associated with worse spatial memory on Arena) and anxiety/arousal (more situational anxiety being related to worse spatial memory on Arena) predictors. Collinearity and residual diagnostics were completed for this model as well. VIF values were less than 1.21, and tolerance values were above .82. No residuals fell outside 3 SD, and all leverage values were .34 or below (most values < .2). These values suggest that the model is robust and relatively uninfluenced by outliers.

Table 5-10. Summary of Hierarchical Regression Analyses for Variables Predicting Spatial Measures in ET.

			Model 1			Model 2		
Spatial Task	*Outcome Variable*	*Predictor Variable*	*B*	*SE B*	*Beta*	*B*	*SE B*	*Beta*
MRT	180-degree error rate	*Constant*	*0.30*	*0.10*		*0.42*	*0.098*	
		Stroop Color-Word	-0.006	0.003	-0.33	-0.006	0.003	-0.37*
		Tremor Severity[a]				**-0.01**	**0.006**	**-0.368***
		R^2		*0.11*			*0.24*	
		F for change in R^2		*3.11*			*4.40*	
C-G Arena	% time in quadrant	*Constant*	*1.88*	*0.46*		*1.8*	*0.42*	
		Age	-0.02	0.005	-0.53	-0.02	0.005	-0.557**
		STAI-State	-0.02	0.005	-0.53	-0.02	0.005	-0.559**
		Tremor Severity[a]				**0.024**	**0.009**	**.392***
		R^2		*0.33*			*0.483*	
		F for change in R^2		*6.16*			*7.06*	

*$p < .05$, **$p < .01$

[a] Based on average TRS scores for left and right upper extremity tremor severity

Summary of Results for the Regression Models

In sum, these analyses indicated that greater severity of tremor in the upper extremities was found to significantly predict spatial functioning (mental rotations and spatial memory) in ET, above and beyond other predictors of performance. Accuracy of mental rotation in the most difficult condition (rotated at 180 degrees) was also positively associated with cognitive inhibition (i.e., the error rate was negatively associated with inhibition). Better spatial memory/navigation was also positively associated with less situational anxiety and younger age.

CHAPTER 6
DISCUSSION

Study Overview and Results Summary

Overview

The first specific aim of this study was to test the counterintuitive but theory-driven hypothesis that severe ET is associated with better spatial cognition than milder ET. A sample of non-demented individuals with an ET diagnosis was recruited and split into two groups, a "mild ET" group with relatively minimal upper extremity intention tremor, and a "severe ET" group with more severe upper extremity intention tremor. A control group of healthy, demographically matched subjects without tremor also was recruited. All participants were tested on a series of visuospatial tasks, with each task assessing predominantly spatial judgments or feature-discrimination / identification, both in the visual domain. This distinction follows Ungerleider and Mishkin's (1982) two streams of visual information processing model, which describes a dorsal stream in the brain that processes spatial information, and a ventral stream that processes form information for purposes of object discrimination / identification. In the present study, the "spatial" tasks measured the following skills: (1) accuracy of judgment for various lines' orientations (JOLO), (2) speed and accuracy for searching a field of similar-looking shapes for a target shape (VST), (3) speed and accuracy for the mental rotation of hand stimuli (MRT), and (4) speed and accuracy for learning the spatial location of an unmarked target in a virtual room (C-G Arena). The "object/form" tasks measured the following skills: (1) accuracy of matching and discrimination of unfamiliar faces (FRT) and (2) speed and accuracy of form-feature judgments for more abstract figures (OAT). The object/form tasks were included along with the spatial tasks primarily to test that differences in visual cognition in mild vs. severe ET are present only when considering spatial abilities (but not other types of visual cognition, such as form/feature-based object identification/discrimination).

Support for Superior Spatial Skills in Severe ET

Comparing the performances of the healthy control, severe ET, and mild ET groups on the visual cognition tasks yielded results that were consistent with hypotheses. First, the severe ET group outperformed the mild ET group on two of the four spatial tasks. More specifically, the severe ET group made fewer errors than the mild ET group on the hardest condition of the mental rotations test (180 degrees / upside-down), whereas the two groups were comparable in speed in this condition. The severe ET group also demonstrated better spatial memory than the mild ET group on the C-G Arena task, based on search behavior during the final (probe) trial, which occurred after the initial learning trials. Of note, the severe and mild ET groups and the controls were statistically equal in age, gender, education, a full scale IQ estimate, situational and generalized anxiety, depressive symptoms, and apathy. The three groups also demonstrated similar ability to use the control pad to navigate as intended on the C-G Arena, and the severe ET group demonstrated the slowest basic reaction time on the CRT. On no task or condition did the severe ET group perform worse than the mild ET group, and none of the mild ET patients performed better than the severe ET patients on any spatial task. Taken together, these findings did not fall contrary to study hypotheses and yielded only supportive evidence.

The second specific aim of this study used regression analysis to determine more specifically whether the better spatial performances in the severe ET group (mental rotations, spatial memory) was related to a factor or factors other than tremor severity.

Again, consistent with hypotheses, tremor severity was found to significantly and positively predict spatial functioning, even beyond the contribution of other significant task-specific predictors (the positive effect of cognitive inhibition). Tremor severity also remained positively predictive of spatial memory, even after accounting for and ruling out the significant, negative effects of age and state anxiety on spatial memory. In sum, this series of analyses provided further evidence that greater disease severity (i.e., arm-related intention tremor) in ET is, paradoxically, predictive of better spatial abilities (i.e., mental rotation of hands and spatial navigation/memory).

The "control" tasks categorized as "object/form" tasks of visual cognition (Facial Recognition Test, Object Attention Task) were administered to demonstrate that tremor severity in ET was associated with spatial skills rather than other types of visual cognition. Indeed, as hypothesized, the severe and mild ET groups performed comparably on these two tests. That is, they were comparable in accuracy for recognition and discrimination of unfamiliar faces, and they were similarly accurate and fast making in feature-based perceptual judgments of overlapping figures. Neither of the two ET groups outperformed controls on these visual object/form tasks.

Some Unexpected Null Findings

While the presence and direction of group differences on two spatial tests was found as hypothesized (i.e., the severe ET group being better than the mild ET group on measures of the mental rotations test and C-G Arena), and the absence of group differences on the two object/form tests were as hypothesized (i.e., the severe ET group performing comparably to the mild ET group in facial recognition and abstract object-feature discrimination), expected differences on two other spatial measures were not observed by group (i.e., JOLO and VST). On the JOLO, The mean raw score and raw corrected score for the severe ET group was comparable to the scores of the mild ET and control groups. The fact that the severe ET group did not demonstrate better performance on this test was contrary to hypotheses and at odds with findings from a previous study. Springer et al. (2006) had found that 19 of 22 pre-surgical ET patients performed above the 50th percentile on this particular test (significantly greater than expected proportion of n/2). In the present study, however, the proportion of patients scoring above the 50th percentile was not significantly greater than the expected value (18 of 30 total ET patients who were tested in the study).

On the VST, the severe ET group did not outperform the other two groups in finding a target shape among distractors; rather, they performed equally, statistically speaking, to the mild ET group and controls. The severe ET group's performance was comparable to the mild ET group's performance on the condition of the task whereby no target was present. This condition was included in the task primarily to ensure the participants were attending to the stimuli and completing the task per instructions (i.e., preventing a strategy of simply pressing the "target" button as soon as the stimuli were visible rather than finding the target). While the severe ET and mild ET groups had similar performances on this condition of the VST, i.e., ruling out the presence of the target, the severe ET group was slower and less accurate than the controls.

Summary

Taken together, this study demonstrated that ET patients with severe upper extremity tremor possess similar or better spatial cognitive skills relative to individuals with mild ET, when demographic factors are comparable and the presence of dementia is ruled out. Better performance was found in the severe ET group on a task of mental manipulation (rotation) of hand representations and another task of spatial navigation/memory. It was not found on other spatial tasks including one measuring perceptual judgment/discrimination of angles, or another involving locating a predefined target shape in a busy field. Moreover, better spatial performance in the severe ET group was found only on select measures within the mental rotations and spatial navigation tasks. It was not found pervasively across conditions on these tests, and when found, the differences were relatively modest in magnitude. On the measures wherein it was observed, however, it was found to be significantly predictive of spatial performance even after controlling for the influence of other significant predictors of performance, such as demographic or fronto-executive abilities. Furthermore, it should be noted that this spatial superiority in the severe ET group was established despite several "cognitive disadvantages" in that subgroup, such as poorer memory and executive functioning. No source for the spatial advantage could be found other than tremor severity.

Although the severe ET group demonstrated evidence for poorer cognitive skills on several *non*-visuospatial measures, there are several other factors that might have contributed to the unexpected lack of group differences as hypothesized (severe ET > mild ET) on the Visual Search Task and Judgment of Line Orientation task. These are discussed below.

Potential Factors Accounting for Unexpected Null Findings

Visual Search Task Factors

A spatial advantage in the severe ET group was not observed on the Visual Search Task. The only group differences that were found included the severe ET group being slower and also making more errors than the control group; this occurred only when the target was not present. The mild ET group, in contrast, performed similarly than controls in this condition. While not overly striking, this pattern of ET group findings relative to controls represents some indirect evidence that the severe ET group may have been slightly worse than the mild ET group in ruling out the presence of a target, although a direct comparison between the two ET groups yielded no differences (on either condition). Even still, further discussion of this pattern of results is warranted.

One possibility for the greater number of non-target errors in the severe ET group (relative to controls) might relate to a higher incidence of simple, executive-motor mistakes, responding with the unintended hand. The overall error rate in this condition was quite low, about 5% of trials, which amounts to two trials over 40 in the non-target condition. If this error rate was artificially high, however, due to unintentional motor responses due to severe postural tremor, then truly high spatial abilities in the severe ET group might have been masked (as well as for the Mental Rotation Task). Indeed, the use of motor-based visuospatial tasks presents a problem for interpretation when used in the assessment of tremor disorders such as ET or Parkinson's disease. The error rate data derived from the Choice Reaction Time task, however, do not converge with the idea that executive-motor errors are higher in the severe ET group. The CRT data show comparable executive-motor error rates on this task when the severe ET group and control groups were compared (about 1.5% of trials). Among the three groups, it was the mild ET group that made more errors on the CRT (right hand), although this error rate was low as well (~3.7%). Thus, it is possible that on the non-target condition of the VST, the group difference in error rate was merely by chance.

The longer response times in the non-target condition for the severe ET group (again, relative to the controls) might have reflected greater "carefulness" in ruling out the presence of the target. Subjectively, the experimenter observed some subjects spontaneously reporting that they were double-checking the screens when the target was not found on an initial scan. The CRT data are consistent with the idea that the severe ET group tended to be more careful in this way: while the severe ET group was motorically slower than the mild ET group on this task, it made significantly *fewer* errors on the CRT as mentioned, with a very low error rate overall (averaging one mistake found for every three severe ET participants who completed the CRT). This explanation likely applies only to the non-target trial findings, however. The severe ET group's error rates and RTs were the same as those for both the controls and the mild ET group in the (main) target condition, and "carefulness" would be reflected by longer response times taken in exchange for lower error rates.

A third possibility might relate to the fact that performance on this hard-feature serial exploratory visual search task more heavily requires efficient object/form recognition in addition to spatial attention. The form/shape of each stimulus in the visual field on this task must be compared with the target shape to determine a "match" or "mismatch", and notably, the targets and two types of distractors had the same "L" shape but different orientations. On non-target trials, the computational load of discriminating between non-target stimuli and the internal representation of the target shape reaches a maximum, as *all* eight non-target stimuli in this condition must be examined to rule out the presence of the target. Thus, any advantage in spatial processing that the severe ET group might possess would potentially be "diluted" by the non-spatial (i.e., object/form perceptual) elements of the VST, with a bias toward more dilution on non-target vs. target trials. Indeed, the authors of this task noted that this task, unlike other feature search tasks, involves non-covert visual searching (i.e., without fixed gaze) in a serial, item-by-item manner (Ellison et al., 2004). A line-bisection or landmark task might have been more appropriate in retrospect, in that such tasks may be more purely “spatial”; this might have yielded group differences in the expected direction.

Finally, a spatial advantage was not observed on the VST in the severe ET group, potentially because of a problem with “domain specificity”. That is, although the VST was chosen for its reliance on right superior temporal gyrus functioning (Ellison et al., 2004; Gharabaghi et al., 2006), an area that Daniels et al. (2006) found to be more cortically dense in severe ET vs. milder ET, it is possible that the relative increase in this area reflected improvement in some other skill related to severe tremor. As pointed out by Daniels et al. (2006), functional neuroimaging studies have shown that this area likely is centrally involved in sensorimotor coordination, the temporal control of movement sequences, goal-directed preparatory activity, and control of polyrhythmic movements (Bengtsson, Ehrsson, Forssberg, & Ullen, 2004; Harrington, Rao, Haaland, Bobholz, Mayer, Binder, et al., 2000; Oullier, Bardy, Stoffregen, Bootsma, & 2004; Toni, Shah, Fink, Thoenissen, Passingham, & Zilles, 2002; Ullen, Forssberg, & Ehrsson, 2003). The adjacently located posterior area of the superior temporal sulcus (pSTS) also is increasingly being appreciated as a center for interpreting biological motion, such as articulated movements or intentional actions (as reviewed by Eysenck & Keane, 2005, and Kolb & Whishaw, 2003). Any or all of these skills might be more consistently practiced in this arm-related intentional tremor disorder via a compensation mechanism (as opposed to visual search for static, relatively meaningless shapes on the VST).

Judgment of Line Orientation Test Factors

It is unclear as to why better performance in the severe ET group was not observed on the JOLO. Springer and colleagues' (2006) study also examined JOLO performance in a severe, older sample of pre-surgical ET patients. Unlike the present study's results, high scores were observed on this test in a disproportionate portion of the sample (19 of 22 patients scoring relatively highly compared to age- and gender-corrected norms). The two study samples were comparable in that they were almost identical in age (70 years) and education (14 years), showed evidence of mild fronto-executive deficits, and similar screening methods were used (i.e., eliminating those with risk factors for generalized cognitive impairment, such as a history of brain injury or failed dementia screening).

It is difficult to make direct comparisons between the present study sample and that tested by Springer et al. (2006), however, as other important information was not available in that earlier retrospective database study. Tremor severity was not measured quantitatively by Springer et al. (2006), a factor that this study suggests is important for predicting spatial functioning. Instead, "severe ET" in the earlier study's sample was only assumed, because the patients were being evaluated for the surgical treatment of presumably impairing tremor. The region of the body affected by ET was not characterized in the earlier study sample, whereas the present study characterized disease severity based on upper extremity tremor. Finally, the medication status of the pre-DBS patient sample tested in the earlier study was not documented. Surgery is typically a treatment option that is reserved for medication-refractory cases, and a relatively unmedicated sample might have been able to perform at a level closer to their true abilities. Superior spatial functioning would have been more evident in such a sample, but these are simply conjectures. In any case, anti-tremor medications, especially in higher doses, can have generalized negative effects (i.e., across tests). Medication status and its potential negative influence on spatial functioning is considered in more detail in the next section. This is followed by a discussion of other “general” factors that could systematically account for poorer-than-expected performance on the JOLO, VST, and other spatial tests.

Anti-Tremor Medications

Two of the most commonly administered pharmacologic agents for the treatment of ET include primidone and propranolol, both of which in higher doses can be associated with mild-to-moderate drowsiness, dizziness, and confusion (Zesiewicz et al., 2008). It is possible that the severe ET group would have outperformed the mild ET group more pervasively across spatial measures, if cognitive side effects of these and other tremor-reducing medications (e.g., alprazolam, topiramate) were a substantial factor in this study. Indeed, deleterious effects of tremor medication on cognition might have accounted for the slightly worse fronto-executive deficits observed in the severe ET group relative to the other groups.

The proportion of the severe ET group that reported taking medications to reduce tremor (11:4, or 73.3%) was not statistically greater than the proportion of the mild ET group reporting the use of anti-tremor medications (9:7, or 56.4%). The proportion was numerically greater in the severe ET group, however, and it is possible that the severe group was taking heavier doses of these medications (or taking more types simultaneously) to treat more severe tremor. If so, cognitive impairment (or even mild cognitive disturbances) due to these medications would be more likely in the severe ET group. In turn, performance accuracy and/or speed would be reduced on spatial measures in this study, potentially masking spatial superiority effects on measures whereby this was not actually observed. Unfortunately, there is no direct method of comparison between the effects of different medications with different doses in different individuals. Participants were asked during screening whether they felt their tremor-reducing medications impacted their thinking. The majority of participants denied this, while the remainder indicated their uncertainty. None definitively indicated this in the affirmative.

Ideally, the participants in this study would have been unmedicated so that the effects of tremor medication could be ruled out. They were not asked to discontinue them prior to their participation, however, because medication washout periods are usually 1-3 weeks in ET studies (e.g., Gironell, Kulisevsky, Barbanoj, Lopez-Villegas, Hernandez, Pascual-Sedano, 1999; Milanov, 2002). This duration of time off medications likely would have hampered ET recruitment efforts substantially, especially for severe ET patients. Although the impact of medications on spatial cognition is only inferred (as disproportionately affecting the severe ET group negatively), this group still outperformed the mild ET group on the mental rotations test and the spatial navigation/memory test.

Motor Requirements

Several efforts were made to minimize any tremor-related effects on experiments using motor-based responses in this study. Tests that lacked motor-based responses were selected when possible, and for the experimental tasks with motor response requirements (i.e., use of the button box or the control pad), the input devices were chosen and placed in such a way that ET participants could minimize the interfering effects of tremor. Control tasks for motor responses were implemented to measure any residual differences. Despite these efforts, the motor-based requirements in the present study potentially represent a methodological limitation to the interpretation of the results. Importantly, these challenges were more likely to interfere negatively with the spatial performances of the severe ET group, thus biasing results away from the directions of the study's hypotheses (i.e., severe ET > mild ET on spatial tasks). Nevertheless, the overall pattern of results might have been clearer if voice- or foot-activated response devices were used for the reaction-time based measures (although the use of these devices would not be free from criticism either).

Theoretical Assumptions of the Study

Functional Organization of the Visual Brain

The fact that only two of four "spatial" tasks yielded findings directly supporting the study hypotheses might be related to incorrect assumptions about the functional organization of the visual brain. The "object/form" and "spatial" task distinction in the present study followed the theoretical distinction between the functions of the ventral (occipito-temporal) and dorsal (occipito-parietal) streams of information processing (Ungerleider & Mishkin, 1982). This model proposes that the ventral stream processes forms, shapes, and/or identity, whereas the dorsal stream processes information about spatial relationships. This "what-where" model was historically influential but not free from criticism in more recent years. From a theoretical standpoint, Ettlinger (1990) noted that objects and forms (e.g., size, shape, pattern) are themselves defined by spatial relationships and therefore these two constructs are fundamentally inextricable for object perception.

Another functional model of the visual brain (Milner & Goodale, 1992; 2009) attempted to address this concern and other limitations of Ungerleider and Mishkin's

(1982) model. Milner and Goodale noted that Ungerleider and Mishkin's (1982) "where" vs. "what" model of visual processing fails to account for more recent findings relating to dorsal stream processing. Their extensive study of a patient with ventral stream damage shows that despite blindness for visual recognition of objects, this patient can "unconsciously" reach for objects and also shape her hand in the correct way for grasping the object, regardless of the object's identity. They also observed that in patients with dorsal stream damage, conscious recognition of objects and their features (including spatial properties) are intact, but there is impairment in manipulating the hands in the correct way during reach-to-grasp tasks. Even in the earlier work upon which Ungerleider and Mishkin based their theory, "spatial" deficits were defined in monkeys who were impaired on reaching and grasping behaviors.

These observations and subsequent, convergent findings led Milner and Goodale (1992) to spearhead a proposal that the dorsal visual stream (which projects toward somatosensory and motor cortices) may be better characterized as a set of systems used for the online, moment-by-moment visual control of action. The ventral visual stream (which projects toward inferior temporal cortex) handles the type of visual perception used in deriving the structure of the environment, such as processing and identifying objects from relatively invariant form-based and spatial properties (Milner & Goodale, 2009). Put simply, these two visual systems are sometimes called the "vision for action" and "vision for perception" streams of processing.

Though not infallible, Milner and Goodale's functional framework might be useful for understanding why the severe ET group outperformed the mild ET group on the C-G Arena and the Mental Rotations Task, but not JOLO or the Visual Search Task. Using this model to reclassify these tests, the C-G Arena task and Mental Rotations Task are, arguably, tests requiring more action-based visual processing. The Visual Search Task and JOLO, on the other hand, are relatively visual-perceptual tasks (as are the previously categorized “object/form” tasks: Object Attention Task and Facial Recognition Test).

Specifically, on the C-G Arena task, spatial memory performance is dependent upon the efficiency of visuomotor control. As they propel themselves forward in the circular arena, participants must use constantly updating visual cues to determine current location and heading (i.e., “optic flow”). They calibrate current direction “on the fly” with fine-motor adjustments in order to guide themselves accurately to the desired location. For these reasons, performance on the C-G Arena seems theoretically reliant on the vision for action system, at least for efficient egocentric navigation (allocentric mapping is mediated more by entorhinal, hippocampal, and parahippocampal cortices).

On the version of the Mental Rotation Task, performance is based on the embodiment and mental, visuomotor manipulation of hand-based stimuli. There was strong evidence that mental rotation of these hands was egocentric and motor based, as suggested by the increasing RTs for conditions requiring more mental rotation (i.e., 180 > 90-in or 90-out > 0 degrees) and those limited by actual biomechanical constraints (i.e., 180 > 90-out > 90-in > 0 degrees) in controls. Arguably, the simplest condition on this task (i.e., 0-degrees) is merely a perceptual condition whereby no mental rotation is performed, and in this condition, the severe ET group did not outperform the mild ET group. This group difference was evident only in the condition that required the greatest degree of mental visuomotor manipulation (i.e., 180 degrees).

These results support the idea that the rotation conditions of the MRT utilize “vision for action” functions. While it might be argued that no overt action actually occurs during the MRT, Glover (2004) described evidence demonstrating that visual planning of action as well as visual control of action both utilize relatively dorsal areas (i.e., superior parietal lobe and inferior parietal lobe, respectively). Other evidence suggests that an inferior parietal area, the superior marginal gyrus, is crucial for motor imagery (mental rotation of hand drawings), whereas the superior parietal lobes is critical for non-embodied visual imagery (mental rotation of letters) (Pelgrims, Andres, & Olivier, 2009). Regardless of the distinction between overt and covert action, in mental rotation, the vision for action pathway (or at least its functional domain) is more heavily involved during performance on hand-based MRT than ventral (perceptual) areas.

In severe forms of ET, then, Milner and Goodale’s (1992) “vision for action” system arguably is the visual system that undergoes the most use and development via compensation for severe arm tremor, relative to milder forms of ET or living without tremor. From a functional perspective, those with severe tremor must expend greater effort in the visuomotor guidance or control of the upper extremities during their use. For this reason, it is perhaps not surprising that group differences were not found on the JOLO and the (serial-perceptual) Visual Search Test (or the Object Attention Task or the Facial Recognition Task), in light of this more updated functional model of the visual brain.

Behavioral Neuroplasticity Driving the Spatial Superiority Effect?

The data supporting behavioral neuroplasticity as the mechanism for (visuomotor) spatial superiority in severe ET is inferred because of limitations to the study design. This study gathered no structural neuroimaging data with which to correlate to spatial performances. Thus, the findings presented by Daniels and colleagues (2006) showing greater cortical density in visuospatial areas (severe ET > mild ET) could not be replicated here, and it was only assumed that this pattern applied to the present study's ET sample. Moreover, no longitudinal data were gathered in this study, rendering impossible any direct relationship between increasing tremor severity and better spatial performances within the same individuals. The cross-sectional design was favored in this study for pragmatic reasons; the time-course of substantially increasing tremor often spans greater than a decade in ET (though as noted above, the trajectory can vary considerably among individuals). Nevertheless, causality cannot be assumed with this correlational design.

Moreover, other potentially influential factors might have accounted for the spatial superiority effect in severe ET (above and beyond tremor severity). The regression analyses attempted to identify factors other than tremor severity that might better account for the visuospatial advantage demonstrated in the severe ET sample. Other potentially causal variables were not measured, and for those that were, the regression analyses were limited a relatively small number of predictors (N=3) because of the small sample size in the study. One small possibility is that the severe ET group happened to possess better spatial skills than the mild ET group even prior to the onset of tremor. This might be ruled out in future studies with an analysis of pre-tremor hobbies, vocations, and/or school subjects. These data were not gathered with enough detail in this study, though it is unlikely to be the case in actuality, given the randomized nature of recruitment, the equal distributions of gender and educational level across groups, the small likelihood that better spatial skills somehow *causes* more severe tremor, and the converging evidence from Springer et al. (2006) and Daniels et al. (2006) as well as the present study that all suggest the positive relationship between arm tremor severity and better spatial skills. Regardless of the mechanism behind the spatial advantage demonstrated in the severe ET group, the phenomenon itself is given more support with these data (especially in conjunction with the previous literature), which suggests that this represents a promising area for further investigation.

Other Directions for Future Research

Additional descriptive studies are needed to replicate this behavioral phenomenon in other ET samples and to more comprehensively describe the parameters under which it operates. There are many outstanding questions. Does the positive relationship between tremor severity and spatial functioning exist on other tasks requiring mental or overt visuomotor manipulation or guidance? Is it only observed on tasks related to the affected area of tremor (upper extremities), or can it be established using other targets of embodiment or control (e.g., the mental rotation of feet, or spatial navigation using foot-operated controls)? Do skills generalize to non-embodied entities (e.g., mental rotation of three-dimensional geometric figures)? One might answer some of these questions by experimentally manipulating both the rotation strategy (egocentric vs. allocentric) and the stimulus type (hands. vs. feet vs. geometric figures).

These and other studies would be relatively theory-driven because it would use the well-supported distinction between “vision for action” vs. “vision for perception” streams of processing. The work by Milner and Goodale (for review, see Milner & Goodale, 2009) used several tasks to test these distinct aspects of vision using patients with well-defined lesions. These can be classified into one or the other category (based on the performance of their patients) and used to test the spatial superiority effect in severe ET. Finally, still other studies might incorporate tasks with more dynamic stimuli and ecological validity. These might aim to determine whether certain spatial advantages have bearing on activities of daily living, for example.

Aside from these additional, theory-driven descriptive studies, future research should attempt to more directly examine neurobiological changes in spatial areas of the brain along with improvements on cognitive / behavioral measures. This might be achieved by using structural and/or functional neuroimaging in tandem with cognitive testing, within the context of a longitudinal design. A longitudinal study design obviously would be laden with several pragmatic challenges, including cost and participant dropout, especially over a relatively (but necessarily) long time period between measurements. One advantage, however, is that behavioral changes could be assessed directly within the same individuals and possibly yield compelling results, especially if tremor severity increases were found to relate to improvements in subtypes of spatial cognition as well as their underlying neural correlates. The pragmatic difficulties, however, may be too restrictive to conduct such a study.

An alternative possibility is to study the relationship between structural brain changes, tremor severity, and spatial cognition in a healthy population. Tremor might be artificially simulated using motorized, weighted mechanisms on the arms, and various tasks could be practiced while this tremor is induced. “Dosage” (i.e., intensity of disturbance) and duration could be manipulated experimentally using this type of paradigm, effectively accelerating the timetable of such a study. This manipulation would also grant more precise experimental control and allow one to characterize the levels of severity and duration of tremor needed to induce a measurable effect in spatial functioning. The use of healthy subjects would allow the experimenter to rule out the effects of medications or neurological conditions, and they would likely be easier to recruit. These and other future studies also would benefit from more objective measurement of intentional tremor. EMG, accelerometers, high-speed video recording, or sensor-based 3-D motion tracking and modeling are several options. This would increase the reliability of this measure and reduce error-related bias.

Aside from the use of healthy controls, additional studies might examine the relationship between tremor severity and spatial functioning in other tremor disorders such as cerebellar stroke or resection, or Parkinson disease (PD). It is intriguing that visuospatial deficits are a common complaint in PD, another age-related movement disorder that, unlike ET, is often characterized by tremor at rest but not during intentional movement (Growdon & Corkin, 1987). Like ET, the characterization of visuospatial functioning in PD probably has been biased toward impairment because of methodological issues including test validity, the use of timed or motor-based measures, or inattention to the cognitive effects of medication status, depression, dementia, or comorbid neurological disease (Crucian & Okun, 2003; Brown & Marsden, 1986; Waterfall & Crowe, 1995). However, high-powered, methodologically well-controlled studies testing a wide range of visual functioning in PD still have demonstrated impairments across even elementary visual-perceptual abilities such as contrast sensitivity, visual/spatial attention, and spatial motion and perception (e.g., Uc, Rizzo, Anderson, Quian, Rodnitzky, & Dawson, 2005). The nature of the relationship between spatial functioning and tremor severity in PD (in the resting tremor subtype) is unclear and could be tested directly to clarify the mechanism of the effect observed in the present study with ET. That is, if increasing severity of resting tremor is associated with visuospatial decline in PD, then this could provide evidence that adjustment to intention tremor is necessary for improvement in spatial skills, consistent with the view presented here that it is the “vision for action” functions that undergo behavioral neuroplasticity. Such a study would need to be well controlled to rule out factors associated with general cognitive impairment.

Significance of the Study

These findings demonstrated for the first time a significant positive contribution of tremor severity for spatial cognition (mental rotation and spatial memory/navigation), above and beyond other predictors. This yielded behavioral evidence that in conjunction with previous behavioral and structural neuroimaging findings is consistent with a compensation / behavioral neuroplasticity hypothesis. That is, it is hypothesized that adjustment to living with intentional arm tremor is associated with improvement of certain action-related visuospatial skills via compensation, and that this improvement is mirrored by brain-related neuroplastic changes. These data imply that cognitive rehabilitation and training visuospatial skills is possible in this and potentially other age-associated neurological populations.

APPENDIX A
TREMOR RATING SCALE

Tremor Rating Scale (TRS)

1. Face Tremor (e.g., jaw)
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude, with chattering
4 - Severe amplitude (rare)

Rest ☐

2. Tongue Tremor
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude

Rest (open mouth) ☐
Post. (protrude) ☐

3. Voice Tremor (read the Rainbow Passage)
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude (unable to speak)

ACT/INT ☐

4. Head Tremor
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude

Rest (against wall) ☐
Post. (unsupported) ☐

5-6. Upper extremity tremor
0 - None
1 - Slight. May be intermittent
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude

	R	L
Rest (arms of chair or on lap)	☐	☐
Post. (extended arms or bent with fingertips together)	☐	☐
ACT/INT (slow finger to nose, fully extended arm)	☐	☐

7. Trunk tremor
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude

Rest (leaning against back of chair) ☐
Post. (unsupported and straight up) ☐

8-9. Lower extremity tremor
0 - None
1 - Slight. May be intermittent.
2 - Moderate amplitude. May be intermittent.
3 - Marked amplitude.
4 - Severe amplitude

	R	L
Rest (sitting and flexed joints at 90 degrees)	☐	☐
Post. (knees fully extended, feet dorsiflexed)	☐	☐
ACT/INT (extend knees to touch target with toes above knee level - 60 degrees)	☐	☐

10-12. Ask the patient to join both points of the varioius drawings without crossing the lines. Test each hand, with the less tremorous hand first, without leaning the hand on the table. Pen should be grasped at the top of with all 4 fingers and thumb, and the pen pointed fairly vertically. Tape the corners of the drawings down (preferred), or use your hand to stabilize it as they draw.

10. Drawing A
0 - Normal.
1 - Slightly tremulous. May cross lines occasionally.
2 - Moderately tremulous or crosses lines frequently.
3 - Accomplishes the task with great difficulty. Many errors.
4 - Unable to complete drawing.

Right ☐
Left ☐

11. Drawing B
0 - Normal.
1 - Slightly tremulous. May cross lines occasionally.
2 - Moderately tremulous or crosses lines frequently.
3 - Accomplishes the task with great difficulty. Many errors.
4 - Unable to complete drawing.

Right ☐
Left ☐

12. Drawing C
0 - Normal.
1 - Slightly tremulous. May cross lines occasionally.
2 - Moderately tremulous or crosses lines frequently.
3 - Accomplishes the task with great difficulty. Many errors.
4 - Unable to complete drawing.

Right ☐
Left ☐

13. Handwriting
0 - Normal.
1 - Mildly abnormal. Slightly untidy, tremulous.
2 - Moderately abnormal. Legible but with considerable tremor.
3 - Markedly abnormal. Illegible.
4 - Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with other hand.

Dom. Hand ☐

14. Pouring (towels, 2 cups, one 2/3 full of water)
0 - Normal.
1 - More careful than a person without tremor but no water is spilled.
2 - Spills a small amount of water (up to 10% of total amount)
3 - Spills a considerable amount of water (> 10 - 50%)
4 - Unable to pour water without spilling most of the water.

Right ☐
Left ☐

Notes:

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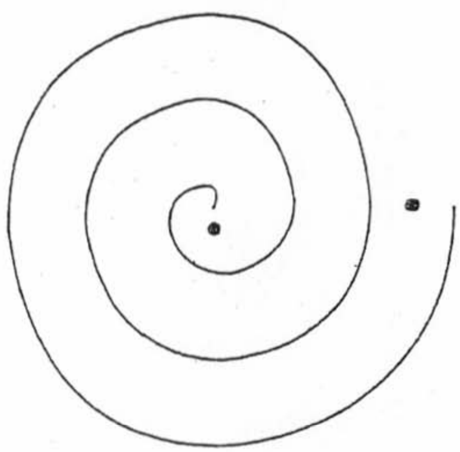
When sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow.

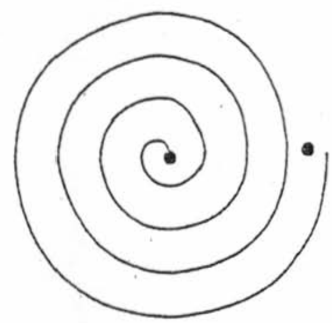
Drawings A, B and C are made with the:

☐ Left Hand ☐ Right Hand

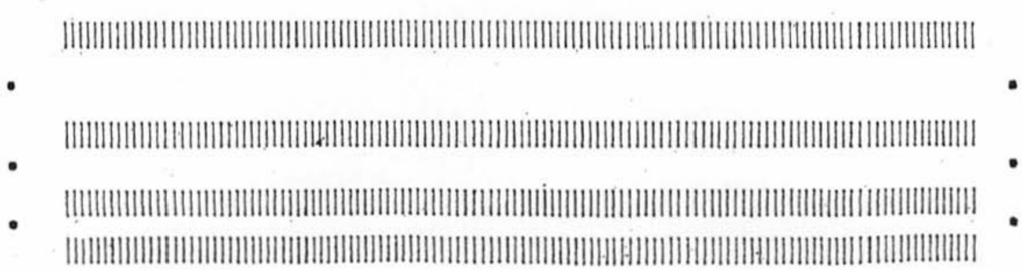
DRAWING A



DRAWING B



DRAWING C



Today is a good day.

____

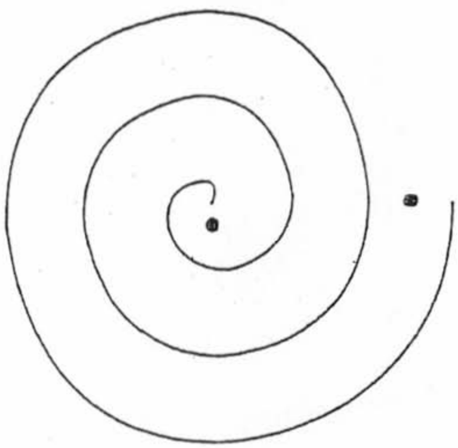
Signature: ____

Date: ____

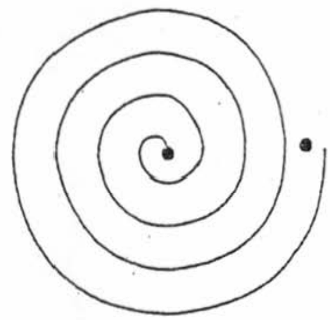
Drawings A, B and C are made

☐ Left Hand ☐ Right Hand

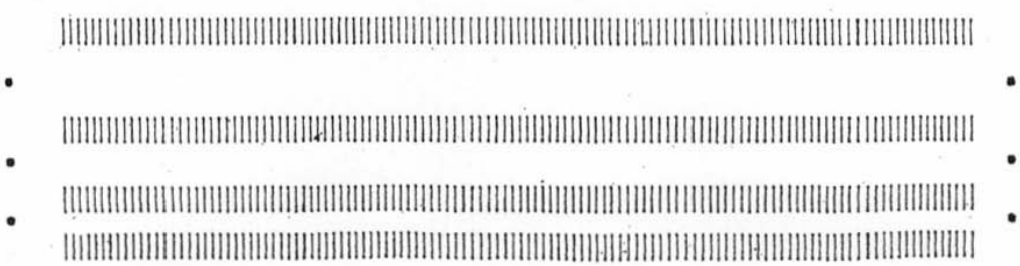
DRAWING A



DRAWING B



DRAWING C



15-21. Activities of Daily Living (interview) AVERAGE FOR PAST WEEK

15. Speaking (this includes spastic dysphonia if present)	0 - Normal. 1 - Mild voice tremulousness when "nervous" only 2 - Mild voice tremor, constant. 3 - Moderate voice tremor 4 - Severe voice tremor. Some words are difficult to understand.	☐
16. Feeding - other than liquids	0 - Normal. 1 - Mildly abnormal. Can bring all solids to mouth, spilling rarely. 2 - Moderately abnormal. Frequent spills of peas and similar foods. May bring head at least halfway to food. 3 - Markedly abnormal. Unable to cut or uses two hands to feed. 4 - Severely abnormal. Needs help to feed.	☐
17. Bringing liquids to mouth	0 - Normal. 1 - Mildly abnormal. Can still use a spoon but not if it is completely full. 2 - Moderately abnormal. Unable to use a spoon; uses cup or glass. 3 - Markedly abnormal. Can drink from cup or glass, but needs two hands. 4 - Severely abnormal, must use a straw.	☐
18. Hygiene	0 - Normal. 1 - Mildly abnormal. Able to do everything but is more careful than the average person. 2 - Moderately abnormal. Able to do everything but with errors, uses electric razor because of tremor 3 - Markedly abnormal. Unable to do most fine tasks such as putting on lipstick or shaving (even with electric shaver) unless using two hands 4 - Severely abnormal. Needs help to feed.	☐
19. Dressing	0 - Normal. 1 - Mildly abnormal. Able to do everything but is more careful than the average person. 2 - Moderately abnormal. Able to do everything but with errors 3 - Markedly abnormal. Needs some assistance with buttoning or other activities such as tying shoelaces 4 - Severely abnormal. Requires assistance even for gross motor activities.	☐
20. Writing	0 - Normal. 1 - Mildly abnormal. Legible. Continues to write letters. 2 - Moderately abnormal. Legible but no longer writes letters. 3 - Markedly abnormal. Illegible. 4 - Severely abnormal. Unable to sign checks or other documents requiring a signature.	☐
21. Working	0 - Tremor does not interfere with job. 1 - Able to work but needs to be more careful than the average person. 2 - Moderately abnormal. Able to do everything but with errors. Poorer than usual performance due to tremor. 3 - Unable to do regular job. May have changed to a different job because of tremor. Tremor limits housework such as ironing. 4 - Unable to do any outside job. Housework very limited.	☐

Global Assessment by Examiner (check one of the 5 levels)

☐ 0	No Functional Disability	1-24% impaired
☐ 1	Mild disability	25-49% impaired
☐ 2	Moderate disability	50-74% impaired
☐ 3	Marked disability	75-100% impaired
☐ 4	Severe disability	

Global Assessment by Patient (check of the 5 levels)

☐ 0	No Functional Disability	1-24% impaired
☐ 1	Mild disability	25-49% impaired
☐ 2	Moderate disability	50-74% impaired
☐ 3	Marked disability	75-100% impaired
☐ 4	Severe disability	

Subjective Assessment by Patient (check one of the 7 levels)

☐ +3	Marked Improvement	50-100% improved
☐ +2	Moderate Improvement	25-49% improved
☐ +1	Mild Improvement	10-24% improved
☐ 0	Unchanged	
☐ -1	Mild Worsening	10-24% worse
☐ -2	Moderate to marked worsening	25-49% worse
☐ -3	Marked worsening	50-100% worse

APPENDIX B
C-G ARENA PARAMETERS AND OBJECT TEXTURES

Visible Targets Trials (Non-Memory Based Motor Control Condition): Parameters

Room, Arena Wall Parameters

Room Width	**Room Depth**	**Room Height**	**Arena Radius**	**Arena Wall Height**	**Arena # of Sides**
150.0	150.0	45.0	50.0	3.50	60

Start Positions / Orientations, Target Positions

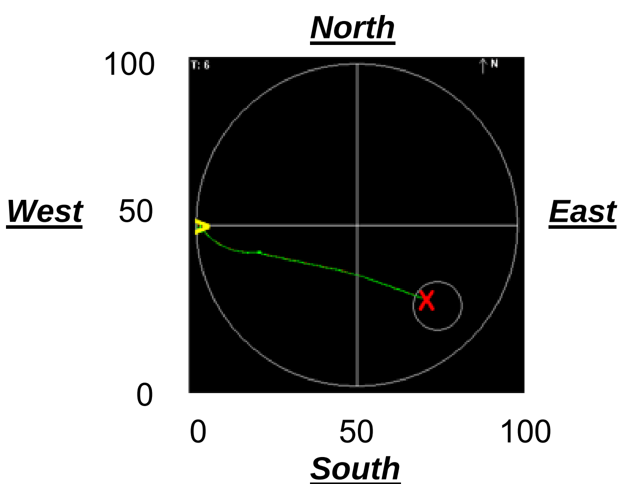
Trial	**Start X,Y***	**Start Area**	**° (Orientation)**	**Target X,Y***	**Location****
Practice	***50,0***	***South***	***0 (North)***	***50,50***	***Center***
1	50,0	South	0 (North)	50,50	Center
2	0,50	West	270 (W)	75,75	Northeast
3	50,100	North	180 (S)	25,25	Southwest
4	100,50	East	90 (E)	25,50	West
5	50,0	South	90 (E)	25,75	Northwest
6	0,50	West	180 (S)	75,25	Southeast
7	50,100	North	270 (W)	75,50	East
8	100,50	East	0 (N)	50,25	South

*Coordinates expressed in percentages of the Arena diameter, with X origin = East, Y origin = South
** Target size is 15x15 and circular in shape

User Parameters

View Height	**Field of View**	**Move Quantum**	**Turn Quantum**
3.00	90.00	0.50	1.50

Room Schematic (example shown = Trial 6)



Legend	**Symbol**
Start/Orientation	>
Example Path	-------
End	X
Target	O

Visible Targets Trials: Object Textures

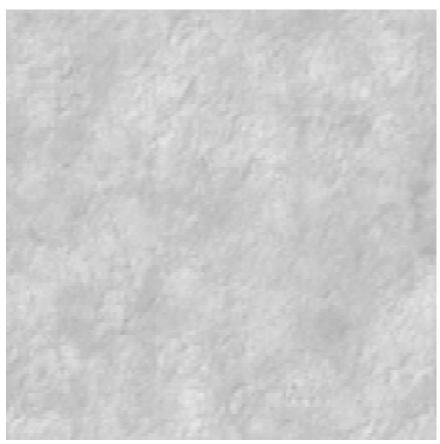
North Wall

East Wall

South Wall

West Wall

Floor



Ceiling

Arena Wall

Hidden Target Trials (Spatial Memory / Navigation Condition): Parameters

Room, Arena Wall Parameters

Room Width	Room Depth	Room Height	Arena Radius	Arena Wall Height	Arena # of Sides
150.0	150.0	45.0	50.0	3.50	60

Start Positions / Orientations, Target Positions

Trial	Start X,Y*	Start Area	° (Orientation)	Target X,Y*	Location**
Practice	***50,0***	***South***	***0 (North)***	***None***	***None***
1	50,0	South	0 (North)	26.5,71.5	Northwest
2	0,50	West	270 (W)	75,75	Northwest
3	50,100	North	180 (S)	25,25	Northwest
4	100,50	East	90 (E)	25,50	Northwest
5	50,0	South	90 (E)	25,75	Northwest
6	0,50	West	180 (S)	75,25	Northwest
7	50,100	North	270 (W)	75,50	Northwest
8	100,50	East	0 (N)	50,25	Northwest
Probe	85,85	Northeast	225 (SW)	None	None

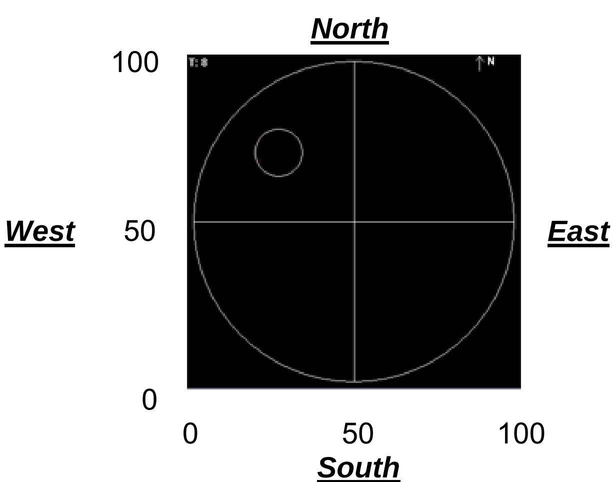
*Coordinates expressed in percentages of the Arena diameter, with X origin = East, Y origin = South

** Target size is 15x15 and circular in shape (when visible, after acquisition)

User Parameters

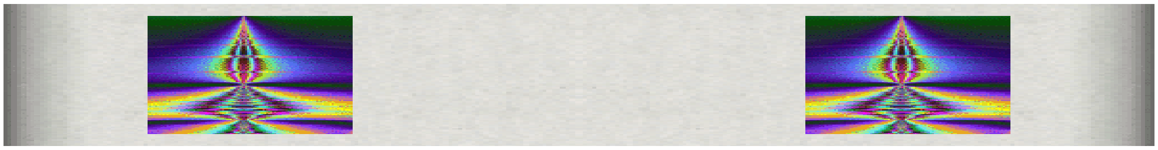
View Height	Field of View	Move Quantum	Turn Quantum
3.00	90.00	0.50	1.50

Room Schematic (hidden target has fixed location)



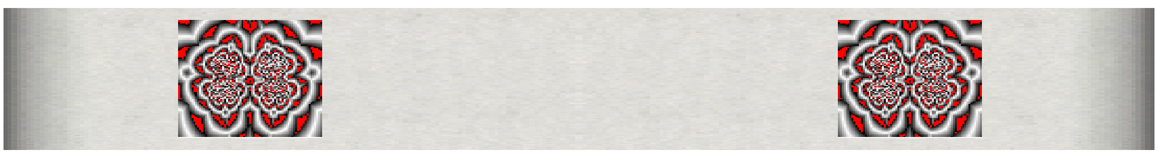
Hidden Target Trials: Object Textures

North Wall

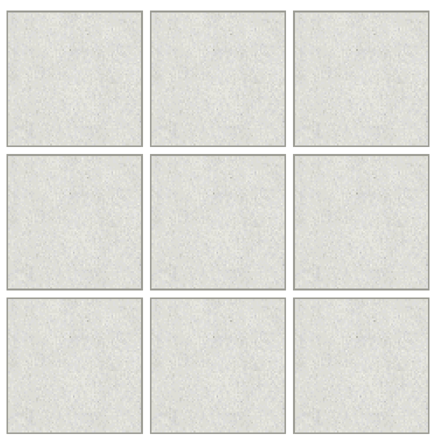


East Wall

South Wall



West Wall



Floor *Ceiling* *Arena Wall*

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BIOGRAPHICAL SKETCH

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