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TOO MUCH TO COUNT ON: IMPAIRED VERY SMALL NUMBERS IN CORTICOBASAL DEGENERATION

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Abstract

Patients with corticobasal degeneration (CBD) have calculation impairments. This study examined whether impaired number knowledge depends on verbal mediation. We focused particularly on knowledge of very small numbers, where there is a precise relationship between a cardinality and its number concept, but little hypothesized role for verbal mediation. We evaluated accuracy and reaction time (RT) for matching dot arrays and Arabic numerals involving smaller (2-4) and larger (5-9) cardinalities in non-aphasic patients with CBD (n=16), frontotemporal dementia (FTD; n=23), and healthy controls (n=15). CBD were less accurate and slowed at judging smaller Arabic numeral-dot array stimuli compared to FTD patients and controls. Moreover, only CBD showed longer RTs judging successively larger number-dot array pairs among the smaller cardinalities. Difficulty judging very small numbers is impaired in CBD, suggesting degraded representation of precise number knowledge that does not depend on language functioning.

Keywords

number; subitizing; corticobasal degeneration; frontotemporal dementia

INTRODUCTION

Number knowledge is a semantic domain for representing the meaning of quantities such as “four” independent of the symbols (4 or IV) or objects (dots, dolls, etc) used to demonstrate this concept (Dehaene, 2000). This parallels modality-neutral approaches to semantic memory for object knowledge (Rogers et al., 2004). Although there are many different approaches to number knowledge (Butterworth, 1999), one hypothesis focuses on the distinction between smaller and larger numbers (Dehaene, 1997). According to this view, small numbers (≤ 4) have a precise mental representation that is independent of the material or modality used to represent the number. The process for recognizing these small cardinalities, called *subitizing*, involves rapid quantification of arrays of objects with little increase in reaction time (RT) as the cardinality increases (Kaufman, Lord, Reese, & Volkmann, 1949). This is said to be distinct from the representation of larger numbers (> 4), where the semantic representation of the corresponding cardinalities is approximate. Any sense of precise number for these cardinalities is thought to depend more on a lexical representation like “nine” or an Arabic numeral like

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“9”. The appreciation of these larger-numbered arrays involves *counting*, a process where each successive cardinality in the number sequence represents an augmentation of the preceding number in the sequence by “1”. The RT for recognizing the cardinality of a larger array increases incrementally as the array increases in size. Of course it may not be possible to detect longer RTs among the smaller cardinalities because the numbers 2-4 are so small. Nevertheless, some evidence for the dissociation between smaller and larger cardinalities comes from observations of animals (Davis & Perusse, 1998; Gallistel, 1989) and prelinguistic infants (Starkey & Cooper, 1980; Wynn, 1992). Furthermore, case reports suggest a double dissociation between subitizing and counting in brain-damaged patients. Insult to the right parietal cortex appears to selectively impair counting while sparing subitizing (Dehaene & Cohen, 1994). Conversely, two patients with developmental dyscalculia demonstrate impaired subitizing but intact counting (Butterworth, 1999; Cipolotti, Butterworth, & Denes, 1991).

In previous reports, we showed that many non-aphasic patients with corticobasal degeneration (CBD) have a deficit with numbers (Halpern et al., 2003; Halpern et al., 2004b; Halpern et al., 2004a). This includes difficulty with oral and written addition of single-digit number pairs, and impaired judgments of relative magnitude in pairs of Arabic numerals, as well as in pairs of dot arrays. This deficit appears to be associated with gray matter atrophy in parietal cortex. Patients with other neurodegenerative diseases such as frontotemporal dementia (FTD) also have difficulty with numbers. This appears to be relatively restricted to larger numbers or to combinatorial processes with greater resource demands such as subtraction and division (Halpern et al., 2003). The aim of the present study is to examine whether very small numbers are more compromised in CBD compared to other patients. If very small numbers have a precise relationship between a cardinality and a number concept, difficulty with small numbers in CBD would be consistent with the degradation of precise number knowledge in a manner that suggests the independence of precise number concepts from language.

METHODS

Subjects

Fifty-four English speakers participated in this study, including 39 patients suffering from neurodegenerative disease and 15 right-handed healthy controls. Demographic and clinical features of these patients are summarized in Table 1. Controls and patients matched in age and education. We assessed overall dementia severity with the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), a 30-point overview of cognitive functioning, and neurodegenerative patients were more impaired than controls. Patients were diagnosed with CBD (n=16) or FTD (n=23) by an experienced neurologist (MG) in the Cognitive Neurology Clinic at the University of Pennsylvania Medical Center. Criteria for CBD, based on clinical-pathological assessments of 27 autopsy-proven cases from our center (Forman et al., 2002; Forman et al., 2006; Murray et al., in press), included the insidious onset and gradual progression of a disorder of parietal lobe functioning such as apraxia, cortical sensory deficit, naming difficulty; and/or asymmetric extrapyramidal features such as alien hand, myoclonus, dystonia and limb rigidity, as well as gait difficulty. There was no evidence for an ocular motility disorder, although two patients did show evidence of mild left-sided neglect. CBD patients had extrapyramidal motor features of varying severity, including 9 of 16 CBD patients with extrapyramidal motor features primarily on the left, 2 of 16 patients with extrapyramidal features more prominently on the right, and 5 CBD patients with fairly symmetric involvement. Although some patients had naming difficulty, Table 1 shows that there was no clinically obvious language comprehension impairment in the CBD patients, demonstrated by a measure of semantic memory. Their performance on a measure of working memory, reverse digit span, was superior to FTD patients. The clinical diagnosis of FTD was based on Lund-Manchester criteria, modified by McKhann et al (The Lund and Manchester Groups, 1994; McKhann et al.,

2001). We examined the role of language in number processing in FTD by dividing this group into those with aphasia, including patients with semantic dementia (SD, $n=8$) and progressive non-fluent aphasia (PNFA, $n=9$), compared to non-aphasic patients with primarily social-behavioral and executive limitations ($n=6$). FTD subgroup diagnosis was based on a consensus evaluation by at least two independent reviewers of the medical record, dividing patients using a modification of criteria by Neary et al (Neary et al., 1998). Other causes of dementia were excluded by history, physical exam, serum studies, and structural brain imaging. Structural and functional neuroimaging, when available, were consistent with the clinical diagnosis. Some patients were taking an acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine), a modest dose of a serotonin-specific re-uptake inhibitor anti-depressant (e.g. sertraline), or an atypical neuroleptic agent (e.g. quetiapine) at a stable dose during testing. Patients were not taking sedating medication. This study was approved by the IRB of the University of Pennsylvania, and all patients and caregivers participated in the Informed Consent procedure.

Materials

Arabic Numeral-Dot Array Matching Task—Patients saw a black square outline in the center of a computer screen filled with an array of large (1 cm diameter) black-filled circles or “dots” against a white background. Simultaneously and directly underneath the array, a single Arabic numeral appeared in black Arial font. Patients were asked to determine if the numerosity of the dot array matched the Arabic numeral in magnitude. We did not test patients using a production task because many of the FTD patients were aphasic. Any patient with asymmetric extrapyramidal motor features affecting an upper limb was asked to use the hand with the least compromised motor functioning when judging arrays. We probed all of the single digit cardinalities from 2 to 9. We excluded arrays of 1 dot from our analyses in order to minimize confusion that seemed to emerge in patients with these stimuli. For purposes of analysis, we divided the dot arrays into “smaller” numbers (2-4) and “larger” numbers (5-9). We presented 144 randomly-ordered stimuli, where half of the dot arrays matched the Arabic numeral in magnitude, and the other half had a numeral-array mismatch that deviated by one or two, although this was limited for the stimulus “2”. An equal number of mismatches involved dot arrays that are larger or smaller than the target Arabic numeral. An equal number of dot stimuli arrayed regularly (like the face of a playing card) and irregularly (randomly) were presented. Within-group comparisons using paired-sample t-tests showed no difference in accuracies between regular and irregular dot arrays for all patient groups. Thus, we combined all regular and irregular stimuli together for the analyses presented below. A Dell PC laptop computer used ePrime v1.1 software to present the stimuli, and record responses and latencies.

Statistical Analysis

We used non-parametric statistical tests to evaluate accuracy because healthy seniors and FTD patients were at or near ceiling in their accuracy judgments. To assess RT differences across groups, we used parametric statistical analyses of correct judgments. Individual performance profiles were analyzed by converting each patient’s accuracy and RT for smaller- and larger-numbered arrays to a z-score relative to the accuracy and RT of the control population.

RESULTS

CBD patients were the most impaired on Arabic numeral-dot array judgments. Table 2 summarizes these findings. According to Mann-Whitney U tests, CBD patients were less accurate judging smaller arrays compared to healthy seniors [$U=35.00$; $p<0.0001$] and FTD patients [$U=89.00$; $p<0.01$]. CBD patients were also less accurate judging larger arrays relative to healthy seniors [$U=32.00$; $p<0.0001$] and FTD patients [$U=80.00$; $p<0.002$]. FTD patients’ did not differ in accuracy from healthy seniors for smaller or larger arrays. Z-score analyses of overall accuracy performance, using a p-value of 0.05 (one-tailed) relative to controls,

showed a significant impairment in 10 (63%) of 16 CBD patients but only 4 (17%) of 23 patients with FTD [$\chi^2(1)=8.34$; $p<0.01$]. Subgroup analyses of FTD did not show any difference in accuracy between the aphasic and non-aphasic group, regardless of array size.

CBD patients required 7.5 seconds to judge the numerosity of small arrays no larger than four dots, over four times longer than controls and twice as long as FTD patients. A repeated measures MANOVA used a between-subject factor of group (3 - CBD, FTD, healthy seniors) and a within-subject factor of numerosity (2 – smaller, larger) to evaluate the RT of correctly judged Arabic numeral-dot array pairs. We found a significant main effect for group [$F(2,51)=13.64$; $p<0.0001$] and a significant interaction effect [$F(2,51)=10.62$; $p<0.0001$]. As summarized in Table 2, CBD patients required longer RTs to judge smaller arrays relative to both healthy seniors [$t(29)=3.82$; $p<0.001$] and FTD patients [$t(37)=3.35$; $p<0.002$]. CBD patients' RTs were slower than both controls [$t(29)=4.30$; $p<0.0001$] and FTD patients [$t(37)=3.24$; $p<0.003$] for judging larger arrays as well. FTD patients showed longer RTs relative to healthy seniors for both smaller arrays [$t(36)=3.08$; $p<0.003$] and larger arrays [$t(36)=3.18$; $p<0.003$]. No difference was found between aphasic and non-aphasic FTD subgroups, regardless of array size.

Only CBD patients demonstrated incrementally longer RTs during judgments of successively larger number-dot array pairs among smaller stimuli, as shown in Figure 1. Analyses of individual patient incremental change in RT, using z-scores to identify abnormal performance at a $p<0.05$ (one-tailed) level relative to the control population, showed that 10 (63%) of the 16 individual CBD patients had significantly longer RTs as array size increased within the smaller number range, although this was found in only 5 (22%) of the 23 FTD patients. A significantly larger proportion of CBD patients than FTD patients thus showed longer RTs to judge smaller numbers as their cardinality increased [$\chi^2(1)=6.62$; $p<0.025$]. No difference between groups was found for larger numbers, where all groups showed longer RTs as the cardinality increased among larger numbers.

DISCUSSION

We find that CBD patients are impaired in their Arabic numeral-dot array matching judgments for cardinalities less than or equal to 4 compared to FTD patients and controls. This deficit is present in a majority of individual CBD patients despite the absence of language comprehension impairment. Even when accurate at judging these smaller arrays, CBD patients require over 7.5 seconds on average to make their judgments. Moreover, as the cardinality increases among these smaller numbers, only CBD patients require increasingly longer latencies to judge cardinalities of increasing magnitude. Thus, their poor understanding of smaller numbers may force them to “count” even the smallest of dot arrays. Numeral-dot array judgments are impaired in FTD relative to controls as well, but these patients rarely show an increase in RTs within the range of very small numbers. These findings are consistent with the hypothesis that CBD patients have a qualitatively distinct impairment with smaller numerosities despite intact language comprehension. Within the range of these smaller arrays, stimuli are said to map precisely onto a cardinality. Difficulty with these smaller numbers despite intact language seems to underline that number knowledge does not necessarily depend on language.

It has been hypothesized that adult humans possess an analogue representation system for number meaning in the form of a mental number line (Dehaene, 1997). Number concepts are arrayed logarithmically on this “mental ruler,” where equal space is devoted to the intervals between 1 and 2, between 2 and 4, between 4 and 8, etc. This has the effect of compressing larger numbers into a smaller, less differentiated space. One consequence is decreasing accuracy and speed during magnitude judgments across the entire set of numbers as the

cardinality increases in magnitude. Another consequence is said to be that larger numbers can be understood in a precise sense only when mediated by a verbal system.

The basis for precise knowledge of smaller cardinalities is less clear. One approach suggests that the same process is used to understand these smaller numbers as is used for the larger cardinalities. The precise meaning of a small number may be easily grasped because of the large amount of space devoted to these small cardinalities on the mental number line (Dehaene, 1997). However, others suggest that small number concepts have a special status (Kaufman, Lord, Reese, & Volkmann, 1949). This distinction is reflected in part in the unique way that very small arrays of objects are subitized. A central characteristic of subitizing is the absence of an increase in RTs to appreciate cardinalities of increasing magnitude within this range of very small numbers. This is distinct from counting, where the RT to appreciate the numerosity of an array increases in a linear manner as the cardinality increases incrementally. We cannot rule out that these very small numbers are counted very rapidly, making it difficult to detect the increase in time as the array increases in size. Support for the claim that the special status of small cardinalities is not verbally mediated nevertheless comes from studies of animals (Davis & Perusse, 1998; Gallistel, 1989) and prelinguistic infants (Starkey & Cooper, 1980; Wynn, 1992). Control subjects and FTD patients, by comparison, showed little latency change with increasing magnitude in the range of small arrays consisting of two to four dots.

While a precise sense of number may be mediated by the word labeling the quantity (Dehaene, 1997), several lines of evidence suggest that the deficit for the precise meaning of smaller numbers in CBD does not depend on verbal mediation. Naming difficulty is reported in clinical series (Grossman et al., 2004; Kompoliti et al., 1998) and in autopsy-proven cases of CBD (Kertesz, Hudson, Mackenzie, & Munoz, 1994; Murray et al., in press; Wenning, Litvan, & Jankovic, 1998), but comprehension single words appears to be relatively preserved (Grossman et al., submitted; Kertesz, Hudson, Mackenzie, & Munoz, 1994; Sakurai, Hashida, & Uesugi, 1996). Moreover, several case studies of brain-damaged patients dissociate language and calculation (Rossor, Warrington, & Cipolotti, 1995; Thioux et al., 1998). The CBD patients examined in the present study are not aphasic. Most CBD patients have greater difficulty in their number knowledge than their performance on a measure of semantic memory for objects (Halpern et al., 2004b). Among FTD patients, moreover, we would expect greater difficulty in the aphasic subgroup if numeral-dot array matching judgments depends on verbal mediation. However, we do not find any difference between aphasic and non-aphasic subgroups of patients with FTD. While additional studies are needed, these observations together suggest a deficit for precise number knowledge that is independent of language functioning.

Patients with CBD may have a visual-spatial impairment (Bak, Caine, Hearn, & Hodges, 2006; Graham, Bak, & Hodges, 2003). This is consistent with neuroimaging (Grossman et al., 2004; Halpern et al., 2004b) and autopsy (Murray et al., in press) evidence for parietal disease in CBD. While the dot arrays involve a spatial component, there is reason to believe that a visuospatial deficit in these patients cannot fully explain their number impairment. In this study, a regular array would make perception of the dots easier for individuals with a spatial deficit, but we do not find any evidence that regularizing the dot array is helpful in CBD. We found previously that magnitude judgments of pairs of Arabic numerals are statistically equivalent to judgments of the relative magnitude of two dot arrays in CBD (Halpern et al., 2004b). Likewise, CBD patients' performance on visuospatial measures does not correlate with their magnitude judgments of pairs of numbers or dot arrays (Halpern et al., 2004a). We also manipulated the visuo-spatial extent of the dots in an array independently of their numerosity by making the dots larger, but patients' numerosity judgments were not affected by the volume of space occupied by an array (Halpern et al., 2004a). Functional neuroimaging studies of calculations and spatial processing in healthy adults show an anatomic dissociation within the

parietal lobe, emphasizing that a deficit in number knowledge need not necessarily accompany a visuospatial deficit (Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002).

CBD patients' extraordinarily long response latencies emphasize their difficulty with this superficially simple task. However, we do not think that an executive impairment can fully explain the qualitative nature of CBD patients' deficit (Graham, Bak, & Hodges, 2003; Pillon & Dubois, 2000), particularly the progressively longer RTs within the range of smaller dot arrays. CBD patients are impaired on reverse digit span, a measure of working memory, but this does not correlate with their calculation impairment (Halpern et al., 2003) or number-dot performance in the present study. CBD patients also do not demonstrate a speed-accuracy trade-off: Their longer latencies are associated with reduced accuracy

CBD patients are also impaired in their performance with larger arrays. Our previous work suggests that this too is due at least in part to their degraded number knowledge (Halpern et al., 2003, 2004b). By comparison, executive resource limitations appear to contribute to the impaired performance of FTD patients. For example, we showed previously a correlation between FTD patients' number-dot judgments and their performance on executive measures such as reverse digit span. This was replicated in the present study. FTD patients also require significantly longer RTs than healthy seniors. However, this may be due in part to a speed-accuracy trade-off, since FTD patients and healthy seniors are equally accurate in their number-dot array matching. Moreover, the qualitative pattern of responding with little change in RT within the subitizing range distinguishes FTD patients from CBD patients. This interpretation is consistent with FTD patients' executive limitations (Kramer, Jurik, & Sha, 2003; Libon et al., in press; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999).

In sum, the present study is compatible with the hypothesis that precise number knowledge is relatively degraded in CBD compared to other patients. Evidence consistent with this claim comes from their impairment profile with very small cardinalities. Since these CBD patients are not aphasic, the deficit in precise number knowledge for these small cardinalities in CBD does not appear to be verbally mediated. We also fail to find a difference in number-dot array matching subgroups of FTD patients with progressive aphasia compared to non-aphasic patients with FTD. These observations underline the dissociation of number knowledge and verbal mediation.

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References

- Bak TH, Caine D, Hearn VC, Hodges JR. Visuospatial functions in atypical parkinsonian syndromes. *Journal of Neurology, Neurosurgery, and Psychiatry* 2006;77:454–456.
- Butterworth, B. *The Mathematical Brain*. London: Macmillan; 1999.
- Cipolotti L, Butterworth B, Denes G. A specific deficit for numbers in a case of dense acalculia. *Brain* 1991;114:2619–2637. [PubMed: 1782535]
- Davis H, Perusse R. Numerical competence in animals: Definitional issues, current evidence and a new research agenda. *Behavioral and Brain Sciences* 1998;11:561–615.
- Dehaene, S. *The Number Sense*. New York, NY: Oxford University Press; 1997.
- Dehaene, S. Cerebral basis of number processing and calculation. In: Gazzaniga, MS., editor. *The New Cognitive Neurosciences*. Cambridge, MA: MIT Press; 2000. p. 987–998.
- Dehaene S, Cohen L. Dissociable mechanisms of subitizing and counting: Neuropsychological evidence from simultanagnosic patients. *Journal of Experimental Psychology: Human Perception and Performance* 1994;29:958–975. [PubMed: 7964531]

- Folstein MF, Folstein SF, McHugh PR. "Mini Mental State." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–198. [PubMed: 1202204]
- Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen H, Van Deerlin VMD, Lee VMY, Miller BL, Trojanowski JQ, Grossman M. Frontotemporal dementia: Clinicopathological correlations. *Annals of Neurology* 2006;59:952–962. [PubMed: 16718704]
- Forman MS, Zhukareva V, Bergeron CB, Chin SSM, Grossman M, Clark C, Lee VMY, Trojanowski JQ. Signature tau neuropathology in gray and white matter of corticobasal degeneration. *American Journal of Pathology* 2002;160:2045–2053. [PubMed: 12057909]
- Gallistel CR. Animal cognition: The representation of space, time, and number. *Annual Review of Psychology* 1989;1989:40–155.
- Graham NL, Bak T, Hodges JR. Corticobasal degeneration as a cognitive disorder. *Movement Disorders* 2003;18:1224–1232. [PubMed: 14639661]
- Grossman M, McMillan C, Moore P, Ding L, Glosser G, Work M, Gee JC. What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia, and corticobasal degeneration. *Brain* 2004;127:628–649. [PubMed: 14761903]
- Grossman M, Moore P, Koenig P, Antani S, McCawley G, Cross K, Kwok S. Semantic knowledge and categorization difficulty: A longitudinal study of Alzheimer's disease and frontotemporal dementia. submitted
- Halpern C, Clark R, McMillan C, Dennis K, Moore P, Grossman M. Calculation difficulty in neurodegenerative diseases. *Journal of the Neurological Sciences* 2003;208:31–38. [PubMed: 12639722]
- Halpern C, Clark R, Moore P, Antani S, Colcher A, Grossman M. Verbal mediation of number knowledge: Evidence from semantic dementia and corticobasal degeneration. *Brain and Cognition* 2004a; 56:107–115. [PubMed: 15380881]
- Halpern C, Glosser G, Clark R, Gee JC, Moore P, Dennis K, McMillan C, Colcher A, Grossman M. Dissociation of numbers and objects in corticobasal degeneration and semantic dementia. *Neurology* 2004b;62:1163–1169. [PubMed: 15079017]
- Kaufman EL, Lord MW, Reese TW, Volkman J. The discrimination of visual number. *American Journal of Psychology* 1949;62:498–525. [PubMed: 15392567]
- Kertesz A, Hudson L, Mackenzie IR, Munoz DG. The pathology and nosology of primary progressive aphasia. *Neurology* 1994;44:2065–2072. [PubMed: 7969961]
- Kompoliti K, Goetz CG, Boeve BF, Maraganore DM, Ahlshag JE, Marsden CD, Bhattia KP, Greene PE, Przedborski S, Seal EC, Burns RS, Hauser RA, Gauger LL, Factor SA, Malha ES, Riley DE. Clinical presentation and pharmacologic therapy in Corticobasal degeneration. *Archives of Neurology* 1998;55:957–961. [PubMed: 9678313]
- Kramer JH, Jurik J, Sha SJ. Distinctive neuropsychological patterns of frontotemporal dementia, semantic dementia, and Alzheimer's Disease. *Cognitive and Behavioral Neurology* 2003;16:211–218. [PubMed: 14665820]
- Libon DJ, Xie SX, Moore P, Farmer J, Antani S, McCawley G, Cross K, Grossman M. Patterns of neuropsychological impairment in frontotemporal dementia. *Neurology*. in press
- McKhann G, Trojanowski JQ, Grossman M, Miller BL, Dickson D, Albert M. Clinical and pathological diagnosis of frontotemporal dementia: Report of a work group on frontotemporal dementia and Pick's disease. *Archives of Neurology* 2001;58:1803–1809. [PubMed: 11708987]
- Murray RC, Neumann M, Farmer J, Forman MS, Johnson JK, Miller BL, Clark CM, Hurtig HI, Lee VMY, Trojanowski JQ, Grossman M. Cognitive and motor assessment in autopsy-proven corticobasal degeneration. *Neurology*. in press
- Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF. Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546–1554. [PubMed: 9855500]
- Pillon, B.; Dubois, B. Memory and executive processes in corticobasal degeneration. In: Litvan, I.; Goetz, CG.; Lang, AE., editors. *Corticobasal Degeneration and Related Disorders*. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 91-101.

- Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW. Specific cognitive deficits in mild frontal variant frontotemporal dementia. *Brain* 1999;122:1469–1493. [PubMed: 10430832]
- Rogers TT, Lambon Ralph MA, Garrard P, Bozeat S, McClelland JL, Hodges JR, Patterson K. Structure and deterioration of semantic memory: A neuropsychological and computational investigation. *Psychological Review* 2004;111:205–235. [PubMed: 14756594]
- Rossor MN, Warrington EK, Cipolotti L. The isolation of calculation skills. *Journal of Neurology* 1995;242:78–81. [PubMed: 7707094]
- Sakurai Y, Hashida H, Uesugi H. A clinical profile of corticobasal degeneration presenting as primary progressive aphasia. *European Neurology* 1996;36:134–137. [PubMed: 8738941]
- Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron* 2002;33:475–487. [PubMed: 11832233]
- Starkey P, Cooper RG. Perception of numbers by human infants. *Science* 1980;210:1033–1035. [PubMed: 7434014]
- The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994;57:416–418.
- Thioux M, Pillon A, Samson D, De Partz M-P, Noel M-P, Seron X. The isolation of numerals at the semantic level. *Neurocase* 1998;4:371–389.
- Wenning GK, Litvan I, Jankovic J. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. *Journal of Neurology, Neurosurgery and Psychiatry* 1998;64:184–189.
- Wynn K. Addition and subtraction by human infants. *Nature* 1992;358:749–750. [PubMed: 1508269]

FIGURE 1. MEAN (S.E.) REACTION TIME TO JUDGE CORRECT ARABIC NUMERAL-DOT ARRAY PAIRS IN CORTICOBASAL DEGENERATION, FRONTOTEMPORAL DEMENTIA, AND HEALTHY CONTROLS¹

NOTE 1. Corresponding z-scores, relative to control subjects, were as follows: CBD: 2: $z = -15.13$; 4: $z = -18.83$; 5: $z = -17.44$; 7: $z = -19.27$; 9: $z = -19.93$; FTD: 2: $z = -3.85$; 4: $z = -3.89$; 5: $z = -5.28$; 7: $z = -5.88$; 9: $z = -6.01$

TABLE 1
MEAN ($\pm$ S.D.) DEMOGRAPHIC AND CLINICAL FEATURES IN CORTICOBASAL DEGENERATION, FRONTOTEMPORAL DEMENTIA AND HEALTHY SENIORS

	Corticobasal Degeneration	Frontotemporal Dementia	Healthy Seniors
N (m/f)	16 (9/7)	23 (13/10)	15 (5/10)
Age (yr) ¹	67.07 $\pm$ 9.82	70.42 $\pm$ 7.69	73.40 $\pm$ 6.91
Education (yr) ¹	15.07 $\pm$ 3.15	14.67 $\pm$ 2.74	15.27 $\pm$ 2.66
MMSE score ¹ (max=30)	21.21 $\pm$ 4.26	22.76 $\pm$ 7.04	29.07 $\pm$ 1.10
Disease Duration (months)	46.91 $\pm$ 20.70	65.75 $\pm$ 25.89	NA
PPT verbal score ² (max=52)	47.62 $\pm$ 3.64	47.58 $\pm$ 4.99	-
Working memory ³	3.56 $\pm$ 1.36	2.95 $\pm$ 1.56	-

¹ T-tests showed that patient groups and controls do not differ at the $p < 0.05$ level for age and education. Patients are worse than controls for MMSE, but FTD and CBD patients do not differ for disease duration, MMSE, or reverse digit span.

² Semantic memory was assessed with the Pyramid and Palm Trees (PPT) task verbal protocol. This is scored as number correct. Only 13 CBD patients and 19 FTD patients were tested on the PPT because of technical difficulties and a data collection oversight. Patients with CBD and FTD have equally modest impairments on PPT. PPT performance did not correlate with number-dot matching accuracy regardless of array size in either CBD patients or FTD patients.

³ Working memory was assessed with the Reverse Digit Span task. This is scored as the number of digits correctly repeated in the reverse order. According to Pearson's correlations, reverse digit span correlated with accuracy judging larger dot arrays [$r = 0.53$; $p < 0.01$], and RTs to smaller [$r = 0.64$; $p < 0.001$] and larger [$r = 0.65$; $p < 0.001$] arrays in FTD, but this measure of working memory did not correlate with number-dot matching performance in CBD.

TABLE 2

MEAN ($\pm$ S.D.) ACCURACY AND REACTION TIME FOR SMALLER AND LARGER NUMBER-DOT ARRAY STIMULI IN CORTICOBASAL DEGENERATION, FRONTOTEMPORAL DEMENTIA AND HEALTHY CONTROLS

	Corticobasal Degeneration	Frontotemporal Dementia	Healthy Seniors
ACCURACY (% CORRECT)			
Smaller	93.62 $\pm$ 9.36	98.28 $\pm$ 3.59	99.62 $\pm$ 1.26
Larger	83.20 $\pm$ 13.51	95.05 $\pm$ 6.87	98.18 $\pm$ 2.52
REACTION TIME (MSEC)			
Smaller	7700.99 $\pm$ 6214.41	3096.31 $\pm$ 1900.72	1520.95 $\pm$ 405.23
Larger	13875.54 $\pm$ 10066.73	6265.99 $\pm$ 4294.66	2691.28 $\pm$ 493.22