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Numerosity Impairment in Corticobasal Syndrome

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Abstract

OBJECTIVE—We assessed the representation of numerosity in corticobasal syndrome (CBS), a neurodegenerative condition affecting the parietal lobe.

METHOD—Patients judged whether a target numerosity (e.g., “3”) falls between two bounding numerosities (e.g., “1” and “5”). We manipulated the format for representing numerosity (Arabic numerals or dot arrays), the size of the gap between the two bounding numerosities, the absolute magnitude of the numerosities, and the order for presenting the bounding numerosities. In a subset of patients with available imaging, we related performance to cortical atrophy using voxel-based morphometry (VBM).

RESULTS—CBS patients were significantly impaired overall (65.7% ±16.2 correct) compared to healthy seniors (96.6% ± 2.4 correct), and required three times longer than controls to judge correct stimuli. This deficit was equally evident for Arabic numeral and dot array formats. Controls were significantly slower with smaller gaps than larger gaps, consistent with the greater challenge distinguishing between numerosities that are more similar to each other than very different numerosities.

However, CBS patients were equally slow and inaccurate for all gap sizes. Controls also were significantly slower with larger numerosities than smaller numerosities, but CBS patients were equally slow and inaccurate with all numerosity magnitudes. VBM revealed significant cortical atrophy in parietal and frontal regions in CBS compared to controls, including the intraparietal sulcus.

CONCLUSIONS—These observations are consistent with the claim that the representation of numerosity is degraded in CBS.

Keywords

number; corticobasal syndrome; intraparietal sulcus

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INTRODUCTION

Number knowledge involves the ordered representation of quantities or amounts, regardless of the symbolic (e.g., Arabic numeral) or non-symbolic (e.g., dot array) format of presentation. The Arabic numeral "5" and the dot array "• • • • •" refer to a quantity that is neither 4 nor 6, but selects precisely for the quantity that is exactly between these (Dehaene, Spelke, Stanescu, & Tsivkin, 1999; Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Hubbard, Piazza, Pinel, & Dehaene, 2005; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002; Venkatraman, Ansari, & Chee, 2005). The neural basis for number knowledge has been studied extensively, largely in functional magnetic resonance imaging (fMRI) assessments of healthy subjects (Ansari, Dhital, & Siong, 2006; Ansari, Lyons, van Eimeren, & Xu, 2007; Dehaene, et al., 1999; Eger, et al., 2003; Fias, et al., 2003; Hubbard, et al., 2005; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Simon, et al., 2002; Venkatraman, et al., 2005. Number knowledge has been linked to parietal and frontal brain regions. In the present study, we evaluated several aspects of numerosity in non-aphasic patients with corticobasal syndrome (CBS), a rare neurodegenerative condition that affects the parietal lobe as well as other brain regions (Murray, et al., 2007). We related performance to regional cortical atrophy using high-resolution structural MRI. We hypothesized that number knowledge – specifically, the mental representation of quantity that is essential to the semantic representation of numerosity – is compromised in CBS.

The nature and representation of number concepts

Arabic numerals and their associated numerosities have multiple properties, and we evaluate several of these in this study. Consider first the format used to represent numerosity. Many believe that there is a single, material-neutral system underlying both symbolic (e.g., "5" or "V") and non-symbolic (e.g., "• • • • •") representations of numerosity (Dehaene, et al., 1999; Eger, et al., 2003; Fias, et al., 2003; Hubbard, et al., 2005; Simon, et al., 2002; Venkatraman, et al., 2005). For example, "five," "5," "V," and "• • • • •" are several ways to represent the concept of "fiveness," and all of these may derive their meaning in part from a deeper, material-neutral representation of quantity. One proposal suggests that numerosity is represented as a kind of mental number line (Dehaene, 1997). In this view, the number line is a material-neutral logarithmic-like scale (e.g., with equal space allocated for the intervals between one and two, two and four, four and eight, etc…) that is the basis for the mental representation of quantity.

fMRI studies frequently show parietal activation, particularly involving the intraparietal sulcus (IPS), for both symbolic (e.g. Arabic numerals) and non-symbolic (e.g., dot arrays) representations of numerosity (Dehaene, et al., 1999; Eger, et al., 2003; Fias, et al., 2003; Hubbard, et al., 2005; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Simon, et al., 2002; Venkatraman, et al., 2005). One fMRI study demonstrated the role of right IPS as the core region involved in representing number quantity by showing increased activation in this area when comparing magnitudes as opposed to simply reading numbers (Chochon, Cohen, van de Moortele, & Dehaene, 1999). Another fMRI study demonstrated activation of bilateral parietal regions during both active and passive viewing of numerosity stimuli, indicating involvement of the IPS independent of task difficulty or attention (Ansari, Dhital, & Siong, 2006).

One way to assess the representation of quantity is with the "distance effect." Pairs of quantities that are relatively close to each other on a mental number line are thought to overlap in their mental representations and share more features than pairs of numerosities that are farther apart. The distance effect is thought to reflect the fact that pairs of numerosities that are closer and have a smaller gap between them are more difficult to discriminate because they share more features than pairs that have a greater separation and have a larger gap between them (Dehaene, Dupoux, & Mehler, 1990; Moyer & Landauer, 1967). Likewise, there is an inverse correlation of reaction time with gap size between pairs of numerosities. Functional neuroimaging studies

have demonstrated that the distance between numbers has a parametric effect on activation in the IPS (Ansari, et al., 2006; Fias, et al., 2003; Pesenti, Thioux, Seron, & de Volder, 2000; Pinel, Dehaene, Riviere, & Le Bihan, 2001). Greater parietal activation thus was found for smaller gaps than larger gaps, presumably reflecting the increased challenge required to discriminate between overlapping numerosities that share many features relative to more distinct numerosities.

There may be a role for format in the processing of numerosity as well. One possibility is that smaller numerosities (i.e., 1 to about 4) are grasped both symbolically and non-symbolically because the representational space for smaller numerosities on the number line is large enough to have meaning as a quantity that is independent of its symbolic representation. By comparison, large numerosities (i.e., greater than about 5) may be more dependent on a symbolic representation because logarithmic compression obscures the representational space of the larger magnitudes and makes it more difficult to distinguish between adjacent larger quantities like 15 and 16 (Dehaene, 1997). From this perspective, the format for representing quantity knowledge may differ depending on the absolute magnitude. Some fMRI evidence supports this claim. One study attributed activation of the left angular gyrus to the verbal mediation needed for larger numerosities (Dehaene, Piazza, Pinel, & Cohen, 2003). Others found subtly lateralized activations depending on the symbolic or non-symbolic nature of the material (Cohen Kadosh, Cohen Kadosh, Kaas, Henik, & Goebel, 2007).

It is also important to consider that smaller numerosities may be processed cognitively in a fundamentally different way than larger numerosities. Smaller numerosities in the range of 1 to about 4 thus may be “subitized” in a very rapid manner that involves simultaneously perceiving an entire array of discrete entities. Perceiving the quantity of an array of discrete entities within the subitizing range thus is said to require the same amount of time, regardless of the magnitude of the array (Kaufman, Lord, Reese, & Volkmann, 1949; Mandler & Shebo, 1982). Subitizing may be rooted in a parallel preattentive visual process that is limited to processing about four or five discrete, non-symbolic stimuli like dot arrays simultaneously (Trick & Pylyshyn, 1994). Evidence for this possibility comes from an fMRI study that differentiated between very small and larger numerosities (Ansari, Lyons, van Eimeren, & Xu, 2007). These authors demonstrated that subitizing activates the right temporo-parietal junction, an area they associated with visuospatial attention. By comparison, arrays of discrete entities greater than about 5 involve “counting.” This is a slower, time-dependent process which relies on serial shifts in spatial attention in order to enumerate an array of discrete entities, and incremental lengthening in the amount of time needed to enumerate the quantity thus is required for each additional item in the array. Unlike subitizing, the time involved in perceiving progressively larger arrays during counting is proportionally longer in a manner that depends on the size of the array. Ansari et al. (2007) found that counting larger numerosities reduced activation in the temporo-parietal junction. From this perspective, there may be an interaction between format and numerosity magnitude because the processing distinction between subitizing and counting may be available only for non-symbolic stimuli but not symbolic stimuli. Others assert that all quantities are counted, regardless of number size. Greater activation was seen in bilateral posterior parietal cortex and dorsal portions of prefrontal cortex during counting as opposed to subitizing (Piazza, Giacomini, Le Bihan, & Dehaene, 2003; Piazza, Mechelli, Butterworth, & Price, 2002), for example, but no areas exhibited significantly greater activation for subitizing relative to counting.

Number quantities are ordered. Letters and months also can be ordered, although these domains are less strongly associated with quantity. fMRI studies describe somewhat equivalent “distance effects” for all domains, including both numbers and letters (Cohen Kadosh, et al., 2008). However, other reports describe dissociations between ordered domains with a prominent quantity dimension and ordered domains with a less prominent quantity feature.

These dissociations are most evident in the frontal lobe. In a task involving order judgments of three kinds of stimuli, greater dlPFC activation was seen in a direct contrast of letters relative to numbers. Letters also showed greater IFC and dlPFC activation than the ordered sizes of geometric shapes, although frontal activation was not seen in the contrast of numbers relative to shapes (Fulbright, Manson, Skudlarski, Lacadie, & Gore, 2003). Silent generation of months, but not silent generation of numbers, resulted in IFC and dlPFC activation (Ischebeck, et al., 2008). Moreover, a direct contrast of these domains revealed greater IFC and dlPFC activation for months. An event-related potential study showed activation of both quantity and order properties of number in parietal regions, while order judgments elicited a greater response in prefrontal regions (Turconi, Jemel, Rossion, & Seron, 2004). One way to examine order takes advantage of an experimental design feature resembling the spatial numerical association of response codes (SNARC) effect. We respond faster to an ordered array of numbers when the smaller numbers are on the left of a number array, for example, and slower when smaller numbers are on the right. This is thought to reflect mapping of left-to-right ascending order to the mental number line (Dehaene, Bossini, & Giraux, 1993; Gevers & Lammertyn, 2005; Hubbard, et al., 2005).

Disruptions of number knowledge following focal brain injury

Acalculia, a term coined by Henschen (Henschen, 1919), is the impairment of number knowledge and difficulty combining numbers using operations such as addition. Numerosity has been examined rarely in neurodegenerative diseases like CBS. A frequent issue in patient studies addresses the relationship between numerosity and language since numerals are mediated verbally. Some studies of patients dissociate number and language, consistent with a distinct neural representation for number knowledge. Several reports describe patients with selective number difficulty on a variety of measures (Cipolotti, Butterworth, & Denes, 1991; Cipolotti, Warrington, & Butterworth, 1995; Lucchelli & De Renzi, 1993; Warrington, 1982). Other studies describe selective language difficulty in the face of preserved number knowledge (Cappelletti, Butterworth, & Kopelman, 2001, 2006; Varley, Klessinger, Romanowski, & Siegal, 2005). In a study of small and large numerosities, a double dissociation between subitizing and counting was suggested in brain-damaged patients (Dehaene & Cohen, 1994), although this may have been confounded by the presence of simultagnosia in patients with lesions to the right parietal lobe. Order has been studied in a small number of case reports as well (Delazer & Butterworth, 1997; Turconi & Seron, 2002). These cases together demonstrated a double dissociation between quantity and ordinal representations of number magnitude. The association between number and order in the SNARC effect has been reported in one patient with Gerstmann syndrome (Mayer, 1999). Mental bisection of orally-presented ordered sequences like numbers and letters also revealed an effect of neglect (Vuilleumier, Ortigue, & Brugger, 2004; Zamarian, Egger, & Delazer, 2007; Zorzi, Priftis, & Umilta, 2002).

However, much work also demonstrates the dependence of number on language, thus challenging the notion that a concept of numeric quantity exists apart from its representation in a symbol system like language. Several reports describe co-occurring arithmetic and language disorders (Dahmen, Hartje, Bussing, & Sturm, 1982; Delazer, Girelli, Semenza, & Denes, 1999). One study demonstrated greater arithmetic impairment in a left hemisphere lesion group compared to a right hemisphere lesion group, despite otherwise intact intellectual abilities (Jackson & Warrington, 1986). A recent group study used Voxel-based Lesion Symptom Mapping to examine the cerebral representations associated with processing language and numbers in left hemisphere stroke patients (Baldo & Dronkers, 2007). The investigators found many areas of overlapping ischemia associated with both arithmetic and language. However, there were also many areas distinctly related to language, and there was

a small area in the angular gyrus of the left parietal lobe associated exclusively with an arithmetic impairment.

Several reports of patients with a rare neurodegenerative condition known as corticobasal syndrome (CBS) have documented a numerosity deficit independent of a language or spatial disorder. CBS is associated clinically with lateralized involuntary movements. These patients have gross atrophy in the parietal lobe that is often accompanied by frontal lobar atrophy. Perhaps the most common cause of CBS is corticobasal degeneration (CBD), a neurodegenerative disease that is associated with atrophy, gliosis and tau-immunoreactive pathology in the gray and white matter of the neocortex, basal ganglia and white matter (Murray, et al., 2007). Other causes of CBS include Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB) (Boeve, et al., 1999). CBS may resemble posterior cortical atrophy (PCA), a visual variant of AD, that is associated with parietal and occipital disease (Alladi, et al., 2007; Benson, Davis, & Snyder, 1988; Mendez, Ghajarania, & Perryman, 2002). These patients have prominent visuospatial difficulty and the emergence of memory deficits over time, but show abnormal involuntary movements less often. Structural neuroimaging studies of CBS (Grossman, et al., 2004) and neuropathologic reports of CBD (Murray, et al., 2007) have found that disease is quite dense in a parietal distribution, although significant disease is also seen in prefrontal areas. Recent work has shown impaired number knowledge and acalculia in non-aphasic patients with CBS. CBS patients thus have difficulty on simple tasks such as magnitude comparisons of pairs of single-digit Arabic numerals or small dot arrays (Halpern, Glosser, et al., 2004). Simple addition, subtraction, multiplication and division of small Arabic numerals or two small arrays of dots is also very demanding for these patients (Halpern, et al., 2003; Halpern, Clark, et al., 2004). In an assessment of subitizing and counting, control subjects required the same amount of time to assess the numerosity of dot arrays in the subitizing range, but showed progressively longer latencies when evaluating the numerosity of increasingly larger arrays. However, CBS patients required more time for each additional numerosity as an array increased in quantity, even within the subitizing range, suggesting difficulty appreciating the numerosity of these very small arrays (Halpern, Clark, Moore, Cross, & Grossman, 2007). CBS patients thus are extraordinarily frustrated when attempting to appreciate dot arrays larger than about 10. These CBS patients were not aphasic, so the deficit could not be attributed to language-based difficulty mediating precise numbers with language. While CBS patients have some visuospatial difficulty, deficits processing number quantity did not correlate with their visuospatial performance. CBS patients were significantly more impaired on these measures than patients with Alzheimer’s disease, emphasizing that dementia per se cannot easily explain the deficit in CBS. Likewise, CBS patients were more impaired than patients with prefrontal disease due to frontotemporal dementia, emphasizing the important role of parietal regions relative to prefrontal regions in assessments of numeric quantity. The deficit on simple measures of numerosity in CBS is doubly dissociated with performance on measures requiring knowledge of objects in patients with semantic dementia (Halpern, Glosser, et al., 2004). Others have reported selectively preserved number knowledge in semantic dementia (Cappelletti, et al., 2001, 2006; Zamarian, Karner, Benke, Donnemiller, & Delazer, 2006). An impairment for numerosity resembling that described in CBS also has been reported in a single case of PCA (Delazer, Karner, Zamarian, Donnemiller, & Benke, 2006). These investigators found an exaggeration of the distance effect in their case.

In the present study we sought to obtain additional information about the deficit in processing numerosity in non-aphasic patients with CBS. We focused on the representation of quantity knowledge associated with numerosity. We did this by devising a “number line” task. This measure involves presenting a target stimulus (e.g., “3”) with two bounding numerosities (e.g., “1” and “5”), and asking participants to judge whether the target stimulus fits between the two bounding stimuli. To examine the integrity of quantity representations, we manipulated the size of the gap between the bounding numerosities. Since CBS patients have difficulty on other

measures involving quantity such as relative magnitude judgment, Arabic numeral-dot array matching, and rapidly enumerating small non-symbolic dot arrays, we also expected them to be impaired on this “number line” task. Moreover, if their knowledge of numerosity is degraded, we would expect CBS patients to not show a “distance effect.” Thus, control subjects should show reduced accuracy and slowed responses with a small gap between bounding stimuli because of overlapping numerosity representations relative to judging a large gap, but CBS patients should be equally impaired with stimuli where a large gap separates the two bounding stimuli and a small gap separates the two bounding stimuli because of their degraded representation of numerosity. Alternately, given the findings of Delazer et al (2006) in a patient with posterior cortical atrophy, it is possible that CBS patients will show an increased distance effect. We also assessed the representation of numerosity in both symbolic (Arabic numerals) as well as non-symbolic (dot arrays) formats. If a central representation of numerosity is impaired, then CBS patients should be equally impaired with symbolic and non-symbolic formats. We also manipulated the absolute numerosity of the stimuli to assess whether numerosity interacts with the symbolic or non-symbolic formats used to represent numerosities. Controls should find smaller numerosities easier to process than larger numerosities because smaller numerosities can be represented in multiple manners including both symbolic and non-symbolic representations while larger numerosities appear to be limited in their ability to be processed when represented in a non-symbolic format (Dehaene, 1997). There are other possible explanations for the magnitude effect (Brysbaert, 2005), although it is beyond the scope of this study to consider all of these. To cite one, if limited subitizing in CBS patients reflects the degradation of very small numerosity representations, and if they are also impaired with larger numerosities because of their difficulty with quantity, then we would expect equal difficulty with small numerosities and large numerosities. Finally, we used an effect resembling the SNARC effect to examine order by manipulating whether the smaller bounding numerosity of a stimulus was presented on the left or the larger bounding numerosity was on the left. If the order component of numerosity is dissociated from the parietal lobe and the representation of quantity, as suggested by case studies that do not confirm the SNARC effect (Gevers & Lammertyn, 2005; Santens & Gevers, 2008) and imaging studies of order (Fulbright, et al., 2003; Ischebeck, et al., 2008; Turconi, et al., 2004), then we would expect that the SNARC effect would be as evident in CBS patients as controls. To supplement our interpretation of performance on these aspects of the number line task, we administered background neuropsychological tests. Thus, we administered other measures of number knowledge, language deficits or visuospatial difficulties to CBS patients. We expected performance on the number line task to be related to measures of number knowledge but not to measures of visuospatial or language functioning. Finally, we used a quantitative image analysis technique, voxel-based morphometry (VBM), to study the anatomic distribution of cortical atrophy in the subset of CBS patients with volumetric MRI images of cortical atrophy. We expected to observe significant cortical atrophy in the parietal lobe of the CBS participants.

METHODS

Subjects

We assessed 10 participants with CBS (5 males and 5 females) and 15 healthy seniors (7 males and 8 females) served as controls. CBS patients (mean ±S.D. age = 66.2 ±8.3 years; education = 13.6 ±3.4 years) were recruited from the outpatient clinic of the Department of Neurology at the Hospital of the University of Pennsylvania and tested in their homes. Experts have suggested specific clinical features important in diagnosing CBS, but there are no published consensus criteria for the clinical diagnosis of this condition. Based on the literature examining clinical-pathologic relations in CBD and our personal experience (Murray, et al., 2007), we developed diagnostic criteria including insidious onset and gradual progression of apraxia, cortical sensory loss and a unilateral extrapyramidal disorder (e.g., myoclonus, rigidity and/or

dystonia), though with little resting tremor. Some of these patients may also have visual perceptual-spatial difficulty or anomia, depending on the laterality of their disease. There was no evidence for an ocular motility disorder or hemi-spatial neglect. Controls were slightly younger (mean ±S.D. age = 58.3 ±5.7 years) and more educated (mean ±S.D. education = 18.8 ±1.7 years; t=4.9; p<0.001) than CBS patients. We found no correlation between education and overall performance on the experimental task.

Neuropsychological Background Measures—To help characterize the CBS patients, we administered a set of standard neuropsychological measures to assessing memory, executive, and language performance. *Mini Mental State Exam (MMSE)* (Folstein, Folstein, & McHugh, 1975) is a non-specific measure of overall dementia severity. *Digit Span forward* (Wechsler, 1987) is a measure of auditory-verbal short-term memory that assesses correct repetition of a list of digits, and *Digit Span Reverse* assesses working memory by monitoring the ability to repeat digits in the reverse order. *Boston Naming Test* (Kaplan, Goodglass, & Weintraub, 1983) is a measure of visual confrontation naming of black-and-white line drawings. *Pyramid and Palm Trees* (Howard & Patterson, 1992) is a measure of associative semantic knowledge using word and picture stimuli. *Category Naming Fluency* (Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994) guided by the target "Animals" is a measure of executive search. *Rey Copy* (Libon, et al., 2007) assesses the patient's ability to copy a modified Rey figure. *Memory Recall* (Libon, et al., 2007) assesses the ability to learn a set of six unrelated words over three trials, and then recall the words after a two-minute delay. *Memory Recognition* is the ability to recognize the six target words when intermixed in a set of six semantically-related foils. Neuropsychological performance is summarized in Table 1. We ensured that subjects could read Arabic numerals by asking them to read aloud the numbers 1–20 presented on paper in a fixed, random order. Patients were also asked to count sets of dots corresponding to the number values 1–10 presented in a random order (n = 10). Subjects also placed Arabic numerals printed on cards and ranging from 1 to 20 in sequential order to test their understanding of the ordinality of a number sequence. Patients could perform these tasks accurately but slowly.

Materials

Number Line Task—Subjects were presented with a target numerosity (e.g., "3") at the top center of the computer screen and two bounding numerosities (e.g., "1" and "5") at opposite sides near the bottom of the screen. The target and the bounding numerosities were separated by a thick horizontal line across the middle of the screen. Subjects were asked to judge whether the target numerosity belongs or fits between the two bounding numerosities using the following instructions: "You will be presented with three numbers. Your task is to determine whether the number above the black line falls between the two numbers below the black line." This was presented in writing while the experimenter read the instructions to the participant. The phrase "sets of circles" was substituted for "numbers" in these instructions prior to presentation of stimuli in a non-symbolic format. Examples of stimuli from screen shots of the computer presenting the stimuli are provided in Figure 1. The location of the target numerosity between the bounding stimuli was equally distributed across the number of available positions within the gap, and the location of the target numerosity outside the gap also was systematically varied. All of the stimuli are provided in the Appendix. To assess an effect for format, the task was presented using symbolic representations (i.e. Arabic numerals, n = 100 trials), with cardinalities ranging from 1–19. We also presented the stimuli in a non-symbolic format with visual dot arrays (n = 60 trials). The dot arrays were presented linearly and oriented vertically to minimize neglect as a confounding factor. We administered only 60 dot arrays to restrict the range of cardinalities to less than 10. Ten is a quantity where prior work and pilot testing showed that CBS patients are willing to enumerate and are less likely to recruit an estimation strategy. CBS patients do not differ in their enumeration and estimation for numerosities up to 8

(McMillan, Clark, Moore, & Grossman, 2006). However, we found considerable reluctance to enumerate on measures like relative magnitude comparison and Arabic numeral-dot array comparison when numerosities larger than about 10 are probed (Halpern, et al., 2003;Halpern, Clark, et al., 2004;Halpern, et al., 2007). The stimuli were presented in a manner blocked by Arabic numeral and dot array format. Within each block, stimuli were presented in a fixed, random order with the ratio of true:false set at 3:2. The Arabic numeral block was administered with a rest half way through the task. Patients were given practice trials prior to administering the number line task to familiarize them with the procedure. This involved the same instructions and 10 trials with each format. Feedback was given following each trial in the practice session to ensure comprehension of the procedure.

Within both the Arabic numeral and dot array formats, we manipulated three factors as described below, including gap size, absolute numerosity, and order:

Gap size: We assessed the integrity of quantity representations by manipulating the size of the gap between the bounding numerosities. Gap sizes used to test a distance effect were classified as small (1, 2, and 3 non-inclusive numerosities between the bounding numerosities; n = 50 numerals, 35 dot arrays), medium (4 and 5 non-inclusive numerosities between the bounding numerosities; n = 24 numerals, 16 dot arrays), or large (6 and 7 non-inclusive numerosities between the bounding numerosities; n = 20 numerals, 15 dot arrays).

Absolute Numerosity: Within each of the small gap sizes, we manipulated the absolute numerosity of the bounding and target stimuli, and classified them as either small (numerosities 1–5; n = 12 numerals, 10 dot arrays) or large (numerosities 5–9; n = 16 numerals, 14 dot arrays). We did this only for small gaps because medium- and large-sized gaps could not generate stimuli that included entirely small or large numerosities due to the larger distance between bounding stimuli (e.g., a gap of 6 would include the bounding numerosities 1 and 6; 1 is a small numerosity and 6 is a large numerosity).

Order: We also assessed the ordered property of numerosities using the SNARC effect. Half of the stimuli at each gap size were presented in a “forward” orientation, with the smaller bounding numerosity on the left side of the screen. The remaining stimuli were presented in the “reverse” order with the larger bounding numerosity on the left of the screen.

Additional neuropsychological background tasks assessing number and visuospatial skills were administered to CBS patients and controls to help understand number line results. We indicate in parentheses below the number of patients where data were available.

***Numerosity Tasks* (n = 10):** These familiar background measures of number knowledge and calculation ability were not intended to replicate the number line task, but instead were administered to ascertain the overall ability to access number representations and process these representations in CBS using common measures. We probed two kinds of calculation operations. We examined subtraction because this requires manipulation of number knowledge with minimal input from an overlearned set of problems and solutions. Subjects were presented with 30 subtraction problems and solutions on the computer screen, and asked to judge whether the solution was correct (e.g., “5 - 3 = 2” at the top of the screen, and “True” and “False” at opposite sides of the bottom of the computer screen). Problems consisted of operands and solutions below 10 in order to minimize carrying or memory demands. Errors only included incorrect solutions that were between 1 and the value of the greater number (e.g., 6 – 4 = 3; 7 – 4 = 5). We also examined multiplication because this may depend in part on an overlearned table of problems and solutions that may be verbally mediated. Subjects were thus presented with 30 multiplication stimuli which followed the same format as the subtraction task except that numerical values of solutions were greater than 10 at times. For multiplication, incorrect

solutions were presented as the value which was one or two steps off of the correct solution on the multiplication table (e.g., 3 × 7 = 18). For each operation, half of the stimuli were correct and half incorrect. We presented these in a manner blocked by operation to minimize errors due to confusing the arithmetic process or switching between arithmetic processes.

In another background numerosity task, subjects were presented with two dot arrays on the computer screen which either differed or had the same number of dots (n = 60 trials). Half of the trials compared spatially organized dot arrays (e.g., as arrayed on the face of dice) and half of the trials compared dot arrays that were organized randomly. Subjects were asked to judge whether the sets contained the same or different number of dots. The dot arrays ranged from 1–9 dots per array and differences between the two arrays under comparison ranged from 1–3 dots. We administered the stimuli in a fixed, random order with the ratio of different:same set at 3:2.

Visuospatial Background Tasks: We assessed visuospatial functioning because CBS patients can have spatial processing deficits, and we sought to determine whether a spatial deficit could explain in part performance on the number line task. In a spatial localization task (n = 7), patients were presented two 4” x 7” rectangles on a page, one above the other. The upper rectangle contained a 1 cm dot. Subjects were asked to draw a dot in the same location in the lower rectangle on the page. We measured the displacement in mm between the center of the target dot and the dot drawn by the patient in the empty rectangle.

The letter cancellation test (n = 10) is a measure of visuospatial attention. Subjects were given 120 seconds to cross off the target letter ‘R’ on a page consisting of 36 ‘R’-letters embedded with 68 ‘non-R’ letters. The target and non-target letters were equally divided among the four quadrants of the page, and randomly distributed within each quadrant. Because of a possible role for visuospatial attention in subitizing performance, we also related letter cancellation performance to number line performance with small numerosities represented in a circle format or an Arabic numeral format.

Procedures

Number line tasks, arithmetic tasks and the dot array comparison task were all presented in this order on computer with subjects responding “yes” or “no” by pressing one of two marked buttons on a computer keyboard. Subjects were allotted 20 seconds to respond with an answer and failure to respond after 20 seconds was marked as incorrect. All other tasks were administered to subjects via pen and paper. This session lasted about 1 hour. Accuracy was monitored for all responses and latency of correct responses was monitored for tasks administered via computer. The neuropsychological battery was administered during a different session lasting about 1 hour, typically within 1 month of the experimental session.

Statistics

We used nonparametric statistics for analysis of number line task accuracy and neuropsychological data because controls performed almost at ceiling on these measures. We used the Mann-Whitney U test for comparisons between CBS and controls, and the Wilcoxon-rank test for comparisons within the CBS and control groups. The Spearman test was used for correlations between CBS performance on the number line tasks and neuropsychological data. We analyzed latencies for correct judgments on number line tasks. We used parametric statistics, including analysis of variance (ANOVA) and t-tests for between-group and within-group analyses. The raw latency data were screened for gross outliers (<1% of responses). Then a 2 S.D. filter was used to screen the remaining data (removing <10% of responses), based on each individual’s mean latency, a procedure that typically yields normally distributed data. Since there was no difference for format (for all levels of all factors, see below), we

combined datasets across the factor of format except where otherwise indicated to assess specific hypotheses.

Imaging

High-resolution structural MRI scans were available to define cortical atrophy in a subset of five CBS patients. We used a modulated version of optimized voxel-based morphometry (VBM). Images were acquired by a SIEMENS Trio 3T MRI scanner. First, a symmetric diffeomorphism procedure was used to normalize high-resolution T1-weighted MR images for shape and intensity (Avants & Gee, 2004) using a local template consisting of 16 healthy seniors and 16 patients. We used high dimensional normalization and template-based cortical segmentation to quantify gray matter changes.

Specifically, a spatially dense mapping, or correspondence, between the template and a population of experimental images was first computed. The brain image was modeled as a dense continuum, sampled at individual voxels and accompanied by a transformation model that preserved neighborhood relationships among voxels even under very large deformations. Moreover, this mapping process was fully unbiased since we used a bidirectional algorithm that builds unbiased maps from the set of experimental brains into a template and, simultaneously, from the template into the population of experimental brains. This bidirectional technique avoided the potential statistical confound associated with traditional, unidirectional mapping that is biased by the nature of the template. The symmetry achieved in this optimization significantly improves normalization compared to unidirectional template mapping (Beg & Khan, 2007). These types of high-dimensional, unbiased maps, called symmetric diffeomorphisms (Avants, Anderson, Grossman, & Gee, 2009; Avants & Gee, 2004), also benefited normalization accuracy because of the reduced variance in the probable location of a structure following deformation. The reduced variance in the estimated location of the neuroanatomy achieved by a symmetric diffeomorphic approach also reduced the amount of smoothing required in the final statistical treatments of these data. The statistical superiority of symmetric diffeomorphisms, relative to available parametric and elastic methods, has been established experimentally in the propagation of neuroanatomic labels across a population of elderly and neurodegenerative brains (Avants, et al., 2009) and in localizing activation in small brain structures such as the hippocampus (Miller, Bege, Ceritoglu, & Stark, 2005).

The resulting images were segmented using FAST (Zhang, Brady, & Smith, 2000), which labels the brain volumes into gray matter, white matter, cerebrospinal fluid, and other with correction for inhomogeneity. Gray matter images were then multiplied by their corresponding jacobian registrations to template space, which resulted in normalized, spatially varying estimates of gray matter volume for each subject (Avants & Gee, 2004). Gray matter images were subsampled to 2mm x 2mm voxel sizes, and then warped into MNI space using the jacobians of the MNI space-warped template. Images were smoothed with a 8mm FWHM Gaussian filter, and contrasted with the cohort of 32 age-matched controls from our control dataset using an independent samples t-test, as described elsewhere (Grossman, et al., 2007). The analysis included all voxels containing any gray matter in the volume, thus resulting in a true whole brain analysis. Implicit masking (e.g., use of a dummy value to exclude voxels with a value of 0) was used to ignore zeros, and global calculation was omitted. We set a statistical threshold for identifying significant gray matter atrophy in the CBS cohort at $p < 0.0002$ level following correction for multiple comparisons with a false discovery rate (FDR) procedure. We included only clusters comprised of 100 or more voxels.

RESULTS

Number line Task

CBS patients (mean ±SD = 65.7% ±16.2 correct) were significantly impaired overall compared to controls (96.6% ± 2.4 correct) ($U = 0.0$, $p < .001$). An analysis of covariance (ANCOVA) demonstrated that this difference between groups remained after co-varying for education [$F(1,23)=32.26$; $p< .0001$). We found that 90% (9/10) of CBS patients are more impaired than the worst control subject ($Z = 12.98$, $p < .05$, according to the binomial test). CBS patients (mean ±SD = 6384 ms ±2263) also took almost three times longer than controls (2348 ms ±555) to judge their correctly answered number line stimuli [$t(23) = 6.68$, $p < .001$]. An analysis of covariance (ANCOVA) again demonstrated that this difference between groups remained after co-varying for education ($F(2,23)= 28.94$; $p < .0001$). This indicates that there was no speed-accuracy trade-off in the patients' judgments, and emphasizes the slowness of CBS patients even when answering correctly.

Arabic Numeral and Dot Array Formats—We found that CBS patients are more impaired than controls with both Arabic numeral and dot array formats, and that there was no difference between formats within the CBS patients or controls. Specifically, the impairment of CBS compared to controls for both formats was evident for small, medium and large gaps, for the small and large absolute numerosities, and for forward and reverse orders (all CBS-control contrasts differed significantly at least at the $p < .007$ level, according to the Mann-Whitney U test, except for small forward Arabic numerals U=51; p=.07, an effect that we showed previously for these overlearned materials (Halpern, et al., 2003). Analyses within CBS also confirmed the equivalence of the formats, as comparisons between formats did not differ significantly at a $p < .05$ level for overall performance or for any of the gap increments (small: z= 1.38; p=.17; medium: z= .26; p=.80; large: z= .53; p= .59), absolute numerosity sizes (small: z= .51; p=.61; large: z= .92; p=.36), or orders of stimulus presentation (forward: z= 1.17; p=. 24; reverse: z= .76; p=.45). Controls also were largely equivalent in their performance across formats for any of the gap increments (small: z= 1.99; p=.05; medium: z= .41; p=.68; large: z= 1.41; p= .16), absolute numerosity sizes (small: z= 1.34; p=.18; large: z= 1.71; p=.09), or orders of stimulus presentation (forward: z= .51; p=.81; reverse: z= 2.21; p=.03). The observation of borderline levels of significance on difficult categories for controls but not CBS patients is consistent with degraded quantity representations in CBS. In the analyses that follow, we describe performance averaged across symbolic and non-symbolic formats except where otherwise indicated.

Gap Size—Figure 2, Panel A summarizes performance at small, medium and large gap sizes. CBS patients were worse than controls for small ($U = 3.0$, $p < .001$), medium ($U = 3.5$, $p < .001$) and large ($U = 1.0$, $p < .001$) gaps. Within-group analyses showed that CBS have equal difficulty with small, medium and large gaps (small vs medium: z= .05; p=.96; small vs large: z = .36; p=.72; medium vs large: z= 1.48; p=.14). This was unlike controls who have less success for small gaps relative to medium (z= 3.36; p=.001) and large (z= 3.41; p=.001) gaps (medium vs large: z=1.16; p=.25). We examined the distance effect in individual CBS patients by comparing accuracy for small gap stimuli relative to large gap stimuli in each patient. We compared this to controls by calculating the average difference between small gap stimuli and large gap stimuli, and we used a threshold of at least 1 standard deviation smaller than that of controls to identify abnormal performance. We found that 6 of 9 CBS cases had a discrepancy between small gap and large gap stimuli that was smaller than that observed in controls. Thus, the distance effect seen in controls was rarely present in individual CBS patients. Indeed, none of the CBS patients had a discrepancy between small gap stimuli and large gap stimuli that was larger than that of controls. Moreover, we found no correlation between disease duration and the discrepancy between accuracy for small gap stimuli and large gap stimuli (r = .26; p=.

46). This suggests an effect for gap size in controls that is not present in CBS and is independent of disease duration.

The effect for gap size in controls but not CBS is confirmed by latency data. As summarized in Table 2, CBS patients took significantly longer than controls to judge stimuli with small, medium and large gaps ($p < .002$ for all gap sizes). Within-group analyses demonstrated that there is a significant difference for gap size latencies in controls, showing slower performance for small relative to medium and large gaps (small vs medium: $t= 5.84$; $p<.001$; small vs large: $t = 8.19$; $p<.001$; medium vs large: $t= 4.37$; $p=.001$). Within CBS patients, latencies did not differ significantly for any gap size at a $p < .05$ level (small vs medium: $t= .16$; $p=.88$; small vs large: $t = .59$; $p=.57$; medium vs large: $t= .05$; $p=.96$). We also found no correlation between disease duration and the discrepancy between latency for small gap stimuli and large gap stimuli ($r = -.14$; $p=.71$). These findings are consistent with a distance effect in controls that is not present in CBS.

One possible strategy that may be adopted by CBS patients is that they are counting small gap stimuli taken from an overlearned sequence of numbers. This would make their performance appear more accurate and faster with small gap stimuli than if forced to rely on assessments of quantity, and from this perspective their performance with small gap stimuli would not differ from the easier, large gap stimuli. We compared performance on the “true” small gap stimuli that can be counted (e.g., 2–3–4) with “false” small gap stimuli where bounding numerosities are separated by a gap of 1 but cannot be counted (e.g., 2–5-4). These two sets of stimuli did not differ in their accuracy ($t=1.07$; $p=.30$) or latency ($t=1.50$; $p=.17$). We also examined performance in CBS patients on the “true” small gap stimuli that can be counted (e.g., 2–3–4) compared to “true” small gap stimuli that cannot be counted (e.g., 2–3–5). These two sets of stimuli also did not differ in their accuracy ($t=1.27$; $p=.23$) or latency ($t=1.92$; $p=.09$). Thus, it is unlikely that the failure to find a discrepancy between small gap stimuli and large gap stimuli is due to CBS patients boosting their performance by counting small gap stimuli.

Absolute Numerosity—Accuracy was more impaired in CBS patients than controls for large ($U = 3.0$, $p < .001$) and small ($U = 23.5$, $p = .001$) numerosities (Figure 2, Panel B). Within-group analyses showed that controls are less accurate for large numerosities relative to their performance with small numerosities ($Z = 3.02$, $p = .003$). An ANOVA with an absolute numerosity X format design in controls confirmed a significant main effect for absolute numerosity ($F(1,14)=19.54$; $p<.001$) but there was no interaction of absolute numerosity with format ($F(1,14)=.007$; $p=.93$). By comparison, CBS patients have equal difficulty with large and small numerosities ($z= 1.17$; $p=.24$). An ANOVA with an absolute numerosity X format design in CBS failed to find a significant main effect for absolute numerosity ($F(1,9)=1.47$; $p=.25$), and there was no interaction of absolute numerosity with format ($F(1,9)=.23$; $p=.63$). This suggests an effect for absolute numerosity in controls that is not present in CBS, and that this effect is present regardless of format.

The effect for absolute numerosity in controls but not CBS is confirmed by the latency data. An ANOVA of response latencies, with a group (2: controls, CBS patients) X format (2: Arabic numeral, dots) X absolute numerosity (2: small, large) design, revealed a main effect for group [$F(1,23) = 39.69$; $p < 0.001$]. We also found a significant main effect for absolute numerosity [$F(1,23)=4.73$; $p<.04$], and a group X absolute numerosity interaction effect that approached significance [$F(1,23)=3.52$; $p=.073$]. As summarized in Table 3, CBS patients took significantly longer than controls to process both small and large absolute numerosities ($p < .001$ for both small and large absolute numerosities). Within-group analyses demonstrated a significant difference for small compared with large absolute numerosity latencies within controls ($t=3.75$; $p = .002$). Within CBS patients, latencies did not differ significantly between small and large numerosities ($t=1.21$; $p=.26$). We did not find a main effect for format [F(1,23)

=.46; p=.50] or an interaction between absolute numerosity and format [F(1,23) = 0.46; p=.50], and neither of these effects interacted with group (p>.97 for both interactions). This suggests degradation of the mental representation of smaller and larger numerosities in CBS patients, and this was present regardless of format.

Order—CBS patients were less accurate than controls for both forward (U = 8.5, p < .001) and reverse (U = 0.0, p < .001) orders of bounding stimulus presentation (Figure 2, Panel C). Within-group analyses showed that both CBS patients (Z = 2.39, p = .01) and controls (Z = 3.41, p = .001) are more impaired for reverse than forward orders of stimulus presentation. This suggests that relative order is treated equivalently in controls and CBS patients.

Neuropsychological Background Tests

Performance on numerosity tasks, including arithmetic, dot numerosity comparisons and dot counting, largely correlated with mean performance on the number line task (Table 4). There is a significant correlation between the number line task and measures involving number skills such as Arithmetic (r=.81; p=.004) and Dot Counting (r=.90; p<.001). This is consistent with the role of number knowledge in CBS patients' performance on the number line task. However, we did not observe a reliable relationship between the format of the number line task and the specific operation used to assess calculations. Thus, multiplication may be mediated in part verbally because of the overlearned nature of the multiplication table, so we examined the correlation between multiplication and performance with the Arabic numeral format of the number line task. This correlation was borderline significant (r=.57; p=.085). It is important to interpret this association cautiously because there is also a correlation between performance with the Arabic numeral format of the number line task and subtraction (r=.58; p=.073). We do not find a correlation between performance with the non-symbolic circle format for the number line task and multiplication (r=.44; p=.2). Moreover there is no correlation between multiplication and number line performance latencies using the Arabic numeral format (r= -.12; p=.74), nor between multiplication and circle number line performance latencies (r=.35; p=.31), nor between subtraction and Arabic numeral number line performance latencies (r= -.26; p=.46). Since subtraction may be less overlearned and more dependent on number knowledge, we also examined the correlation between subtraction and number line performance using a non-symbolic circle format. This correlation was not significant for accuracy (r= .50; p=.13) or latency (r= .19; p=.59).

We examined the correlation between number line performance and performance on visuospatial tasks, including dot spatial localization and letter cancellation. However, these were not significant (see Table 4). Since subitizing may be mediated in part by visual attention, we also examined the correlation between letter cancellation and performance on small numerosity stimuli from the number line task. There is no correlation between letter cancellation and small numerosity number line stimuli using a circle format (r= .27; p=.48) or an Arabic numeral format (r=.24; p=.53). Thus, there appears to be a minimal role for visual attention in judgments of numbers in the subitizing range in CBD.

Imaging

Significant atrophy in five of the CBD patients is illustrated in Figure 3. The peak loci in each of the clusters are summarized in Table 5. The critical feature in our findings was significant atrophy in the IPS bilaterally as well as prefrontal regions.

DISCUSSION

Our observations are consistent with the hypothesis that the mental representation of numerosity is profoundly degraded in CBS. The impairment on the number line task in CBS

was equally evident with a symbolic format – Arabic numerals – and a non-symbolic format – circle arrays. We assessed the integrity of the mental representation of numerosity by examining the distance effect with gap size. While controls demonstrated significantly shorter latencies and increasing accuracy as the size of the gap became larger and the numerosity features overlapped less, CBS patients were equally impaired with small, medium and large gaps. This was regardless of format. The absence of an interference effect from overlapping numerosities suggests that the mental representation of numerosity is degraded in CBS. We also examined the role of absolute numerosity. Controls were significantly more successful with small relative to large numerosities, but CBS patients demonstrated equal difficulty with small and large numerosities. This was regardless of format. This too is consistent with impoverished verbal and visuospatial representations of numerosity in CBS. CBS patients and controls were equal in their relative difficulty with bounding numerosities presented in a reverse order of presentation compared to a forward order of presentation. This suggests that the order component of number knowledge is relatively preserved in CBS. This impairment profile in CBS was associated with significant cortical atrophy in the IPS as well as other regions of the parietal and frontal lobes. Our findings should be interpreted cautiously because of the small number of CBS patients participating in this study and because of educational differences between CBS patients and controls. We discuss these findings in greater detail below.

CBS patients were profoundly impaired in their performance on the number line task. They were only 65.7% correct on this very simple judgment. Even in their accurate judgments, the CBS patients required over 6 seconds on average to judge whether a target number like “3” is between the numbers “1” and “5.” This impairment was widespread, seen in 90% of individual CBS patients. Patients were equally impaired with Arabic numerals and dot arrays. Their performance generally correlated with familiar measures involving number knowledge. We showed previously that patients with CBS are impaired on measures of numerosity such as relative magnitude judgments, Arabic numeral-dot array matching, subitizing, and calculations with numerosities in the single digit range (Halpern, et al., 2003; Halpern, Clark, et al., 2004; Halpern, et al., 2007; Halpern, Glosser, et al., 2004). Some of the materials required processing of non-symbolic numerosities that are distributed in a visuospatial array, and CBS patients have some difficulty on measures of visuospatial processing. Nevertheless, their performance on the number line task did not correlate with measures of visuospatial functioning. The task itself does not appear to be too difficult for CBS patients because they did not differ from controls for small Arabic numerals. Likewise, the deficit cannot be attributed easily to non-specific dementia since the mean MMSE score of the CBS patients was in the mild range. Their performance on other neuropsychological measures also indicated that they do not have a generalized dementia. Prior work has shown that CBS patients are more impaired than patients with Alzheimer’s disease on measures involving number knowledge (Halpern, et al., 2003). The present study thus confirms observations of difficulty with numerosity in CBS.

The failure to observe an effect for gap size in CBS is consistent with the observation that the mental representation of numerosity is degraded in these patients. Gap size reflects the distance effect, where numerosities relatively close to each other are thought to share features and therefore to be more challenging to discriminate than numerosities that are further apart on a number line (Dehaene, et al., 1990; Moyer & Landauer, 1967). Sensitivity to gap size thus is a robust way to examine the integrity of numerosity representations because the interference between relatively similar numerosities in the distance effect can only occur if the numerosity is clearly represented. CBS patients did not differ significantly across the gap sizes we assessed, either in their accuracy or their latency. Delazer et al (2006) described an increased effect for gap size in a case study of a single patient with PCA, a condition that has parietal-occipital disease typically due to AD. A majority of individual CBS patients in the present study showed an effect for gap size that was smaller than that seen in controls, and we never observed an

increased effect for gap size as seen in Delazer's (2006) case. This inconsistency may be due to the different ways in which the distance effect was examined in the two studies, to the different distributions of disease in PCA compared to CBS, or to a difference in the presumed pathology associated with PCA and CBS. Future work directly comparing CBS and PCA directly with an identical technique will be needed to resolve this discrepancy between studies. Accuracy for the various gap sizes was almost at ceiling levels in controls in the present study, potentially limiting the statistical interpretability of accuracy results, but controls nevertheless demonstrated significantly longer latencies in processing relatively smaller gaps compared to larger gaps. It is possible for controls to adopt many different strategies for judging the target relative to the two bounding numerosities (Nuerk, Geppert, van Herten, & Willmes, 2002; Wood, et al., 2008). For example, controls can develop an algorithm that calculates the average of the bounding numerosities and compare this to the target numerosity. Although calculations with smaller numbers may be performed more rapidly than with larger numbers for several reasons (Zbrodoff & Logan, 2005), an algorithmic strategy would not necessarily explain the finding of relatively slower performance with stimuli exhibiting a smaller gap since a calculating algorithm should show no distance effect because the same calculations are required regardless of distance. Another possible strategy is that subjects can count from one bounding numerosity to the other and determine whether the count includes the target numerosity. However, we examined a counting strategy empirically, and we found no evidence to support counting in CBS. Another possibility is that subjects can approximate. In a previous study assessing quantifier meaning (McMillan, et al., 2006), CBS patients were asked to judge the truth value of a sentence like "At least 3 of the balls are red" relative to an array of familiar objects. CBS patients were significantly impaired on this task. An analysis of error patterns revealed that performance did not differ under conditions where precise determination or general approximation were possible strategies. Regardless of the specific basis for controls' performance, CBS patients appear to be unable to adopt a strategy that reflects the distance effect seen in controls, namely, slower and less accurate performance for closer numerosities that overlap in their numerosity representations. Future work on the distance effect should evaluate these strategies systematically. We did not examine the location of the target numerosity within the gap in a large enough amount to allow statistical analyses. This would be important to examine in future studies.

Our observations are consistent with a single system underlying both symbolic and non-symbolic representations of numerosity (Dehaene, et al., 1999; Eger, et al., 2003; Fias, et al., 2003; Hubbard, et al., 2005; Piazza, et al., 2007; Simon, et al., 2002; Venkatraman, et al., 2005). Thus, we did not find a difference in performance with Arabic numerals and dot arrays in CBS. There has been considerable debate about the role of the format used to present assessments of numerosity. For example, some have claimed that a sense of quantity depends in part on a symbolic or verbal system for identifying precise numerosity, particularly for larger numerosities (Dehaene, et al., 2003). Studies of patients have not been able to resolve this issue (Baldo & Dronkers, 2007; Cappelletti, et al., 2001, 2006; Dahmen, et al., 1982; Delazer, et al., 1999; Lucchelli & De Renzi, 1993; Varley, et al., 2005). We used both symbolic Arabic numeral and non-symbolic dot array formats in the administration of the number line task reported in this study. We found parallel effects for Arabic numerals and dot arrays. This was evident in assessing gap size, assessments of absolute numerosity, as well as the interaction of these two factors. CBS patients may have been able to use a visuo-perceptual strategy, associating a longer perceptual line of dots with a larger numerosity. However, CBS patients could not take advantage of this visuo-perceptual cue. In previous work, we found no statistical advantage for dots arrayed in a structured manner that might be amenable to a visuo-perceptual strategy compared to dots arrayed randomly (Halpern, et al., 2003; Halpern et al., 2007). Mean performance on the number line task largely correlated with other measures of numerosity such as arithmetic and dot counting. We examined the possibility that multiplication is an overlearned, verbally-mediated process and thus correlated with number line performance in

the Arabic numeral format but not the non-symbolic format. However, our findings did not support this preferential association of multiplication with a symbolic format. We speculate that the preferred verbal format for multiplication may reflect in part an artefact of the overlearned multiplication table in Western society, and this effect is lost in CBS patients who have degraded number knowledge and thus are less capable of taking advantage of the multiplication tables. Additional work is needed to resolve discrepancies such as this.

CBS patients did not demonstrate an interaction between format and absolute numerosity. This observation is inconsistent with the hypotheses relating visuospatial attention to the representation of very small numerosities during subitizing (Ansari, et al., 2007; Trick & Pylyshyn, 1994), or a verbal-symbolic format to the representation of larger numerosities that may require mediation by verbal material (Cohen Kadosh, et al., 2007; Dehaene, et al., 2003). Consider first the possibility that a verbal-symbolic format interacts with absolute magnitude in the representation of larger numerosities (Cohen Kadosh, et al., 2007; Dehaene, et al., 2003). From this perspective, only a symbol system such as Arabic numerals can represent larger numerosities in a manner that can be used for precise representations of numerosity and computations because of logarithmic compression of larger numerosities on the mental number line. Larger numerosities thus may depend more on left parietal symbolic representations. Smaller numerosities may be grasped both symbolically using a left parietal mechanism and non-symbolically in right parietal cortex because of the larger space available for representing smaller numerosities on the mental number line. Evidence to support this format-specific approach comes from an fMRI study implicating the left angular gyrus in precise arithmetic computations (Dehaene, et al., 2003), and a recent fMRI report suggesting a subtle, material-dependent laterality effect in numerosity processing (Cohen Kadosh, et al., 2007). We failed to find such an interaction between format and absolute numerosity. Our data are consistent with neuroimaging studies that have failed to demonstrate format-specific representations of numerosity lateralized to the left or right parietal lobe (Dehaene, et al., 1999; Eger, et al., 2003; Fias, et al., 2003; Hubbard, et al., 2005; Piazza, et al., 2007; Simon, et al., 2002; Venkatraman, et al., 2005). One possible confound in our study is that CBS patients did not have aphasia, thus potentially biasing against the inclusion of CBS patients with left parietal disease. However, the imaging data show disease bilaterally in the intraparietal sulcus. A format-specific deficit for reading Arabic numerals has been reported (Cipolotti, et al., 1995), but the present study did not assess performance with other symbolic stimuli (e.g., Roman numerals) or other modalities (e.g., spoken numerals) (Baldo & Dronkers, 2007; Dehaene & Changeux, 1993). Additional work is needed to assess the full range of formats and modalities for representing smaller and larger numerosities in a larger group of CBS patients.

There is another sense in which absolute numerosity may interact with format in the representation of quantity. Smaller arrays of dots in the range of 1 up to about 5 thus nay be subitized, or processed simultaneously by a visual preattentive mechanism for the rapid enumeration of small numerosities (Kaufman, et al., 1949; Mandler & Shebo, 1982). This contrasts with numerosities larger than about 5 that may be counted, or processed in a serial manner that increases the numerosity by 1 during ordered enumeration of the series (Ansari, et al., 2007; Feigenson, Dehaene, & Spelke, 2004; Trick & Pylyshyn, 1994; Xu & Spelke, 2000). Subitizing requires an equal amount of time for rapidly processing any numerosity within the subitizing range, while counting requires incrementally more time for processing a numerosity in proportion to its quantity. Evidence consistent with the distinction between subitizing and counting comes from a study showing activation in right parietal-occipital cortex, an area associated with visuospatial attention, while subitizing very small numerosities (Ansari, et al., 2007). In the present study, we found that control subjects are more rapid in their performance with smaller than larger absolute numerosities. This is consistent with subitizing in controls, although the absence of an interaction effect with format raises the

possibility of other explanations such as the possibility that subitizing is implemented at a conceptual level involving magnitude under some circumstances rather than the spatial representation of visual stimuli. However, CBS patients did not show a difference in accuracy or latency as a function of the absolute magnitude of a numerosity, and there was no interaction of format with absolute numerosity. Moreover, accuracy with small numerosity stimuli did not correlate with performance on the visual attention letter cancellation test in CBS for either format, implying that CBS patients are not employing a visuospatial, attention-mediated strategy to process smaller numerosities. This is consistent with prior observations suggesting that CBS patients, unlike controls, use a single, incremental process like counting to assess the entire range of numerosities (Halpern, et al., 2007). Even though performance with sequential gap stimuli is not different from performance with non-sequential stimuli, this does not necessarily mean that these patients cannot count or use a counting strategy for other tasks involving quantity. Counting was not presented explicitly as a strategy for performing the number line task in this study, for example, and the stimuli were not arrayed to evoke counting. CBS patients have some difficulty on visuospatial tasks, but no correlation was found between performance on visuospatial tasks such as dot spatial localization and the number line task (Halpern, et al., 2007). It is important to exercise caution when interpreting our findings since they do not address the alternative proposal that healthy adults process all numbers via counting (Piazza, et al., 2002), where small numbers may be counted too quickly to be detected. Although the role of visual attention in subitizing has been emphasized in some previous work (Ansari, et al., 2007; Trick & Pylyshyn, 1994), our findings suggest that additional factors should be considered in explanations of subitizing phenomena.

We studied order by manipulating the left-to-right presentation of bounding numerosities, resembling the SNARC effect. Both controls and CBS patients demonstrated similar profiles of relative difficulty with the reverse order compared to the forward order. This suggests that the ordered property of numerosity is not necessarily compromised in CBS. However, this is only an indirect examination of the ordered property of numerosity since it trades on the overlearned left-to-right scanning strategy evident in cultures using English and related languages. Additional work is necessary to evaluate the ordinal component of numerosity representations in a more direct manner.

CBS patients had significant atrophy in the IPS region of the parietal lobe. Previous imaging work found a similar distribution of disease in CBS (Grossman, et al., 2004; Halpern, Glosser, et al., 2004), and autopsy observations emphasize parietal disease in CBS (Murray, et al., 2007). Previous fMRI work demonstrated reliable parametric increases in parietal activation as the distance between pairs of compared numerosities decreases, and IPS activation has been seen during other numerosity tasks (Ansari, et al., 2006; Fias, et al., 2003; Pesenti, et al., 2000; Pinel, et al., 2001). Our study thus is consistent with a role for number knowledge in the IPS region of the parietal lobe. Functional neuroimaging work in adults (Cohen Kadosh, et al., 2008; Piazza, et al., 2003; Piazza, et al., 2002; Pinel, et al., 2001) also has provided evidence consistent with numerosity representation in frontal cortex. Patients with CBS have disease in the frontal lobe as well. We cannot entirely rule out the contribution of frontal disease to the numerosity deficit in CBS. A prior report described difficulty on measures of Arabic numeral-dot array matching and calculation in patients with prefrontal disease due to frontotemporal degeneration (Halpern, et al., 2003; Revkin, et al., 2008), but the deficit in these patients was significantly milder than in patients with CBS (Halpern, et al., 2003). Our sample of patients with quantitative imaging was too small to perform a reliable analysis directly relating cortical atrophy to performance on the number line task, and additional work is needed in the future to establish the neuroanatomic basis for the numerosity impairment in CBS.

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REFERENCES

Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, et al. Focal cortical presentations of Alzheimer's disease. Brain 2007;130(10):2636–2645. [PubMed: 17898010]

Ansari D, Dhital B, Siong SC. Parametric effects of numerical distance on the intraparietal sulcus during passive viewing of rapid numerosity changes. Brain Research 2006;1067(1):181–188. [PubMed: 16359648]

Ansari D, Lyons IM, van Eimeren L, Xu F. Linking Visual Attention and Number Processing in the Brain: The Role of the Temporo-parietal Junction in Small and Large Symbolic and Nonsymbolic Number Comparison. Journal of Cognitive Neuroscience 2007;19(11):1845–1853. [PubMed: 17958487]

Avants B, Anderson C, Grossman M, Gee J. Symmetric normalization for patient-specific tracking of longitudinal change in frontotemporal dementia. Medical Image Analysis. 2009 in press.

Avants B, Gee JC. Geodesic estimation for large deformation anatomical shape and intensity averaging. Neuroimage 2004;23:S139–S150. [PubMed: 15501083]

Baldo JV, Dronkers NF. Neural correlates of arithmetic and language comprehension: A common substrate? Neuropsychologia 2007;45:229–235. [PubMed: 16997333]

Beg MF, Khan A. Symmetric data attachment terms for large deformation image registration. IEEE Transactions for Medical Imaging 2007;26:1179–1189.

Benson DF, Davis RJ, Snyder BD. Posterior cortical atrophy. Archives of Neurology 1988;45:789–793. [PubMed: 3390033]

Boeve BF, Maraganore DM, Parisi JE, Ahlskog JE, Graff-Radford NR, Caselli RJ, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999;53:795–800. [PubMed: 10489043]

Brysbaert, M. Number recognition in different formats. In: Campbell, JID., editor. Handbook of Mathematical Cognition. New York: Taylor & Francis; 2005. p. 23-42.

Cappelletti M, Butterworth B, Kopelman MD. Spared numerical abilities in a case of semantic dementia. Neuropsychologia 2001;39:1224–1239. [PubMed: 11527560]

Cappelletti M, Butterworth B, Kopelman MD. The Understanding of Quantifiers in Semantic Dementia: A Single-Case Study. Neurocase 2006;12:136–145. [PubMed: 16801149]

Chochon F, Cohen L, van de Moortele PF, Dehaene S. Differential contributions of the left and right inferior parietal lobules to number processing. Journal of Cogitive Neuroscience 1999;11:617–630.

Cipolotti L, Butterworth B, Denes G. A specific deficit for numbers in a case of dense acalculia. Brain 1991;114:2619–2637. [PubMed: 1782535]

Cipolotti L, Warrington EK, Butterworth B. Selective impairment in manipulating Arabic numerals. Cortex 1995;31:73–86. [PubMed: 7540123]

Cohen Kadosh R, Cohen Kadosh K, Kaas A, Henik A, Goebel R. Notation-dependent and -independent representations of numbers in the parietal lobes. Neuron 2007;53:307–314. [PubMed: 17224410]

Cohen Kadosh R, Lammertyn J, Izard V. Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. Progress in Neurobiology 2008;84:132–147. [PubMed: 18155348]

Dahmen W, Hartje W, Bussing W, Sturm W. Disorders of calculation in aphasic patients - spatial and verbal components. Neuropsychologia 1982;20:145–153. [PubMed: 6178056]

Dehaene, S. The Number Sense. New York, NY: Oxford University Press; 1997.

Dehaene S, Bossini S, Giraux P. The mental reepresentation of parity and number magnitude. Journal of Experimental Psychology: General 1993;122:371–396.

Dehaene S, Changeux JP. Development of elementary numerical abilities: a neuronal model. J. Cognit. Neurosci 1993;5:390–407.

Dehaene S, Cohen L. Dissociable mechanisms of subitizing and counting: Neuropsychological evidence from simultagnosic patients. Journal of Experimental Psychology: Human Perception and Performance 1994;29:958–975. [PubMed: 7964531]

Dehaene S, Dupoux E, Mehler J. Is numerical comparison digital? Analogical and symbolic effects in two-digit number comparison. J. Exp. Psychol. Hum. Percept. Perform 1990;16:626–641. [PubMed: 2144576]

Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. Cognitive Neuropsychology 2003;20:487–506.

Dehaene S, Spelke ES, Stanescu R, Tsivkin S. Sources of mathematical thinking: Behavioral and brain-imaging evidence. Science 1999;284:970–974. [PubMed: 10320379]

Delazer M, Butterworth B. A dissociation of number meanings. Cognitive Neuropsychology 1997;14:613–636.

Delazer M, Girelli L, Semenza C, Denes G. Numerical skills and aphasia. Journal of the International Neuropsychological Society 1999;5:213–221. [PubMed: 10217921]

Delazer M, Karner E, Zamarian L, Donnemiller E, Benke T. Number processing in posterior cortical atrophy - A neuropsychological case study. Neuropsychologia 2006;44:36–51. [PubMed: 15936044]

Eger E, Sterzer P, Russ MO, Giraud AL, Kleinschmidt A. A supramodal number representation in human intraparietal cortex. Neuron 2003;37:719–725. [PubMed: 12597867]

Feigenson L, Dehaene S, Spelke E. Core systems of number. Trends in Cognitive Sciences 2004;8:307–314. [PubMed: 15242690]

Fias W, Lammertyn J, Reynvoet B, Dupont P, Orban GA. Parietal Representation of Symbolic and Nonsymbolic Magnitude. Journal of Cognitive Neuroscience 2003;15(1):47–56. [PubMed: 12590842]

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]

Fulbright RK, Manson SC, Skudlarski P, Lacadie CM, Gore JC. Quantity determination and the distance effect with letters, numbers, and shapes: A functional MRI imaging study of number processing. American Journal of Neuroradiology 2003;23:193–200. [PubMed: 12591633]

Gevers W, Lammertyn J. The hunt for SNARC. Psychological Science 2005;47:10–21.

Grossman M, Libon DJ, Forman MS, Massimo L, Wood E, Moore P, et al. Distinct Antemortem Profiles in Patients With Pathologically Defined Frontotemporal Dementia. Arch Neurol 2007;64(11):1601–1609. [PubMed: 17998442]

Grossman M, McMillan C, Moore P, Ding L, Glosser G, Work M, et al. 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]

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 2004;56:107–115. [PubMed: 15380881]

Halpern C, Clark R, Moore P, Cross K, Grossman M. Too much to count on: Impaired very small numbers in corticobasal degeneration. Brain and Cognition 2007;64:144–149. [PubMed: 17397978]

Halpern C, Glosser G, Clark R, Gee JC, Moore P, Dennis K, et al. Dissociation of numbers and objects in corticobasal degeneration and semantic dementia. Neurology 2004;62:1163–1169. [PubMed: 15079017]

Henschen SE. Uber sprach- musik- und rechenmechanismen und ihre lokalisationen im grosshirn. Zeitschrift fur die Gesante Neurologie und Psychiatrie 1919;52:273–298.

Howard, D.; Patterson, K. Pyramids and Palm Trees: A Test of Semantic Access from Pictures and Words. Nature Publishing Group; 1992.

Hubbard EM, Piazza M, Pinel P, Dehaene S. Interactions between number and space in parietal cortex. Nat Rev Neurosci 2005;6(6):435–448. [PubMed: 15928716]

Ischebeck A, Heim S, Siedentopf C, Zamarian L, Schocke M, Kremser C, et al. Are numbers special? Comparing the generation of verbal materials from ordered categories (months) to numbers and other categories (animals) in an fMRI study. Human Brain Mapping 2008;29:894–909. [PubMed: 17705220]

Jackson M, Warrington EK. Arithmetic skills in patients with unilateral cerebral lesions. Cortex 1986;22:611–620. [PubMed: 3816245]

Kaplan, E.; Goodglass, H.; Weintraub, S. The Boston naming test. Philadelphia: Lea and Febiger; 1983.

Kaufman EL, Lord MW, Reese TW, Volkmann J. The discrimination of visual number. American Journal of Psychology 1949;62:498–525. [PubMed: 15392567]

Libon DJ, Massimo L, Moore P, Coslett HB, Chatterjee A, Aguirre GK, et al. Differentiating the frontotemporal dementias from Alzheimer's disease: The Philadelphia Brief Assessment of Cognition. Dementia and Geriatric Cognitive Disorders 2007;24:441–447. [PubMed: 17971665]

Lucchelli F, De Renzi E. Primary dyscalculia after a medial frontal lesion of the left hemisphere. Journal of Neurology, Neurosurgery and Psychiatry 1993;56:304–307.

Mandler G, Shebo BJ. Subitizing: An analysis of its component processes. Journal of Experimental Psychology: General 1982;11:1–22. [PubMed: 6460833]

Mayer E. A pure case of Gerstmann syndrome with a subangular lesion. Brain 1999;122:1107–1120. [PubMed: 10356063]

McMillan CT, Clark R, Moore P, Grossman M. Quantifier comprehension in corticobasal degeneration. Brain and Cognition. 2006 in press.

Mendez MF, Ghajarania M, Perryman KM. Posterior cortical atrophy: Clinical characteristics and differences compared to Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2002;14:33–40. [PubMed: 12053130]

Mickanin J, Grossman M, Onishi K, Auriacombe S, Clark C. Verbal and non-verbal fluency in patients with probable Alzheimer's disease. Neuropsychology 1994;8:385–394.

Miller MI, Bege MF, Ceritoglu C, Stark C. Increasing the power of functional maps of the medial temporal lobe by using large deformation diffeomorphic metric mapping. Proceedings of the National Academy of Sciences of the USA 2005;102:9685–9690. [PubMed: 15980148]

Moyer RS, Landauer TK. Time required for judgments of numerical inequality. Nature 1967;215:1519–1520. [PubMed: 6052760]

Murray R, Neumann M, Forman MS, Farmer J, Massimo L, Rice A, et al. Cognitive and motor assessment in autopsy-proven corticobasal degeneration. Neurology 2007;68:1274–1283. [PubMed: 17438218]

Nieder A, Diester I, Tudusciuc O. Temporal and spatial enumeration processes in the primmate parietal cortex. Science 2006;313:1431–1435. [PubMed: 16960005]

Nieder A, Freedman DJ, Miller EK. Representation of the quantity of visual items in the primate prefrontal cortex. Science 2002;297:1708–1711. [PubMed: 12215649]

Nieder A, Miller EK. Coding of cognitive magnitude: compressed scaling of numerical information in the primate prefrontal cortex. Neuron 2003;37:149–157. [PubMed: 12526780]

Nieder A, Miller EK. A parieto-frontal network for visual numerical information in the monkey. Proc. Natl Acad. Sci. USA 2004;101:7457–7462. [PubMed: 15123797]

Nuerk H-C, Geppert BE, van Herten M, Willmes K. On The Impact of Different Number Representations in the Number Bisection Task. Cortex 2002;38(5):691–715. [PubMed: 12507040]

Pesenti M, Thioux M, Seron X, de Volder A. Neuroanatomical substrates of arabic number processing, numerical comparison, and simple addition: A PET study. Journal of Cognitive Neuroscience 2000;12:461–479. [PubMed: 10931772]

Piazza M, Giacomini E, Le Bihan D, Dehaene S. Single-trial classification of parallel pre-attentive and serial attentive processes using functional magnetic resonance imaging. Proc. R. Soc. Lond. B 2003;270:1237–1245.

Piazza M, Mechelli A, Butterworth B, Price CJ. Are subitizing and counting implemented as separate or functionally overlapping processes? Neuroimage 2002;15:435–446. [PubMed: 11798277]

Piazza M, Pinel P, Le Bihan D, Dehaene S. A magnitude code common to numerosities and number symbols in human intraparietal cortex. Neuron 2007;53:293–305. [PubMed: 17224409]

Pinel P, Dehaene S, Riviere D, Le Bihan D. Modulation of parietal activation of semantic distance in a number comparison task. Neuroimage 2001;14:1013–1026. [PubMed: 11697933]

Revkin SK, Piazza M, Izard V, Zamarian L, Karner E, Delazer M. Verbal numerosity estimation deficit in the context of spared semantic representation of numbers: A neuropsychological study of a patient with frontal lesions. Neuropsychologia 2008;46(10):2463–2475. [PubMed: 18502452]

Santens S, Gevers W. The SNARC effect does not imply a mental number line. Cognition 2008;108(1): 263–270. [PubMed: 18313655]

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]

Trick LM, Pylyshyn ZW. Why Are Small and Large Numbers Enumerated Differently? A Limited-Capacity Preattentive Stage in Vision. Psychological Review 1994;101:80–102. [PubMed: 8121961]

Turconi E, Jemel B, Rossion B, Seron X. Electrophysiologic evidence for differential processing of numerical quantity and order in humans. Cognitive Brain Research 2004;21:22–38. [PubMed: 15325410]

Turconi E, Seron X. Dissociation between order and quantity meanings in a patient with Gerstmann syndrome. Cortex 2002;38:911–914.

Varley RA, Klessinger NJC, Romanowski CAJ, Siegal M. Agrammatic but numerate. Proceedings of the National Academy of Sciences 2005;102

Venkatraman V, Ansari D, Chee MW. Neural correlates of symbolic and non-symbolic arithmetic. Neuropsychologia 2005;43:744–753. [PubMed: 15721187]

Vuilleumier P, Ortigue S, Brugger P. The number space and neglect. Cortex 2004;40:399–410. [PubMed: 15156797]

Warrington EK. The fractionation of arithmetic skills: A single study. Quarterly Journal of Experimental Psychology 1982;34:31–51. [PubMed: 7201657]

Wechsler, D. Wechsler memory scale - revised. San Antonio: The Psychological Corporation; 1987.

Wood G, Nuerk H-C, Moeller K, Geppert B, Schnitker R, Weber J, et al. All for one but not one for all: How multiple number representations are recruited in one numerical task. Brain Research 2008;1187:154–166. [PubMed: 18022606]

Xu F, Spelke ES. Large number discrimination in 6-month-old infants. Cognition 2000;74:B1–B11. [PubMed: 10594312]

Zamarian L, Egger C, Delazer M. The mental representation of ordered sequences in visual neglect. Cortex 2007;43:542–550. [PubMed: 17624000]

Zamarian L, Karner E, Benke T, Donnemiller E, Delazer M. Knowing 7 × 8, but not the meaning of 'elephant': Evidence for the dissociation between numerical and non-numerical semantic knowledge. Neuropsychologia 2006;44:1708–1723. [PubMed: 16697429]

Zbrodoff, NJ.; Logan, GD. What everyone finds: The problem-size effect. In: Campbell, JID., editor. Handbook of Mathematical Cognition. New York, NY: Psychology Press; 2004. p. 331-345.

Zhang Y, Brady M, Smith S. Hidden Markov random field model for segmentation of brain MR images. SPIE Proceedings 2000;3979:1126–1137.

Zorzi M, Priftis K, Umilta C. Neglect disrupts the mental number line. Nature 2002;417:138–139. [PubMed: 12000950]

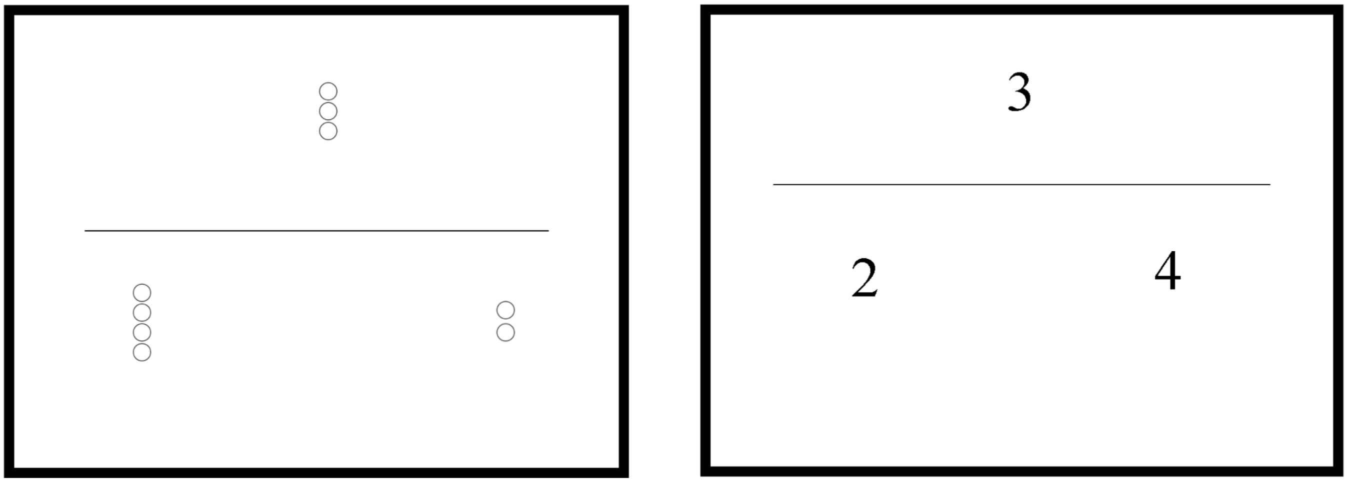

Figure 1.
Display of Arabic Numeral and Dot Array Stimulus Presentation.

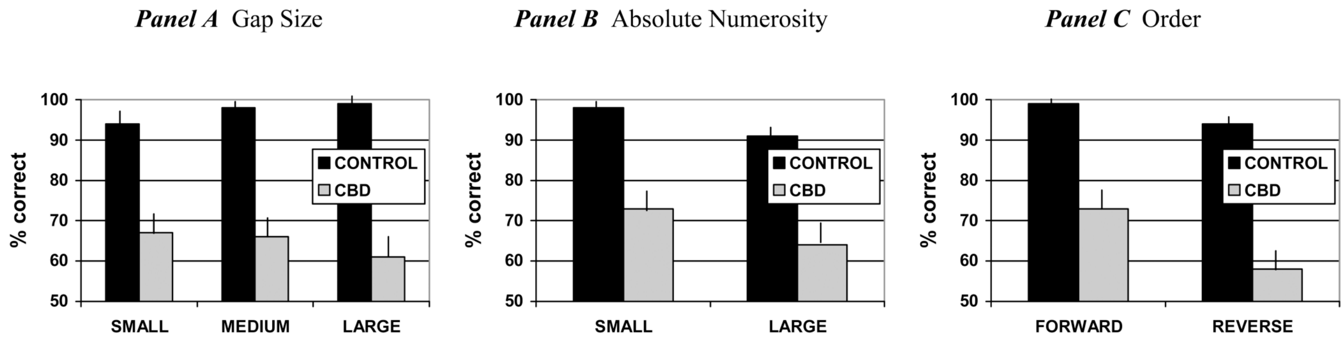

Figure 2.
Mean Accuracy for Gap Size, Absolute Numerosity, and Order in Patients with Corticobasal Syndrome (CBS) and Controls

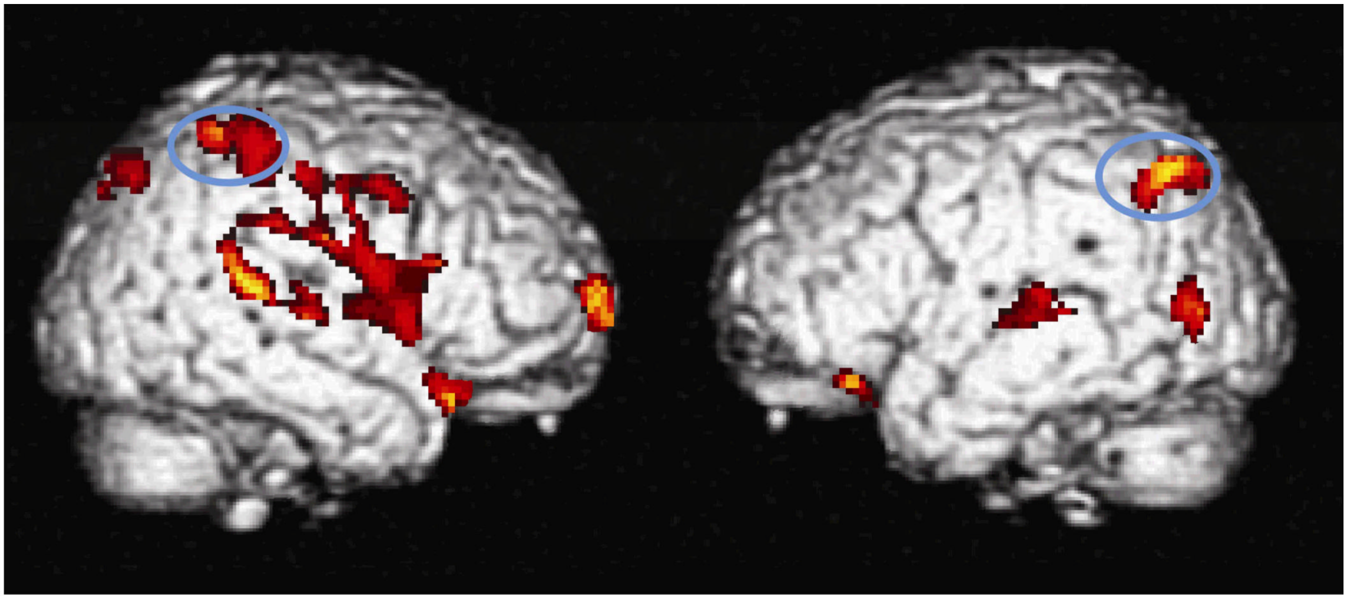

Figure 3.
Regional Cortical Atrophy in Corticobasal Syndrome1
NOTE
1. Blue circles indicate atrophy in the intraparietal sulcus.

TABLE 1

Mean (standard deviation) neuropsychological measures in corticobasal syndrome patients[1]

MMSE (/30)	20.90 ±6.14
DIGIT SPAN FORWARD (max repeated correctly)	5.88±1.64
DIGITS SPAN REVERSE (max repeated correctly)	3.56±1.81
BOSTON NAMING TEST (% accuracy)	68.89±16.58
PYRAMID AND PALM PICTURES (max=52)	44.88±7.99
PYRAMID AND PALM WORDS (max=52)	46.11±5.15
ANIMAL FLUENCY (max in 60 sec)	7.67±4.64
MODIFIED REY FIGURE COPY (max=12)	5.11±4.16
VERBAL MEMORY RECALL (max=6)	3.56±2.35
VERBAL MEMORY RECOGNITION (max=3)	2.28±0.94

NOTE

[1]Nine CBS patients performed these measures. The tenth patient could not be assessed due to unforeseen circumstances, and one CBS patient did not perform the Pyramid and Palm Pictures condition.

TABLE 2

Mean (standard deviation) latency of responses to small, medium and large gap stimuli for corticobasal syndrome (CBS) patients and controls

	CBS	Control
Small Gap (ms)	6533 (2286)	2504 (579)
Medium Gap (ms)	6491 (2459)	2271 (582)
Large (ms)	6131 (2362)	2008 (504)

TABLE 3

Mean (standard deviation) latency of responses to small and large nunerosity stimuli for corticobasal syndrome (CBS) patients and controls

	CBS	Control
Small Magnitude (ms)	6334 (6579)	2345 (626)
Large Magnitude (ms)	6684 (6788)	2698 (692)

TABLE 4

Correlations of number line performance with numerosity and visuospatial tasks in corticobasal syndrome (CBS)

		CBS Performance (Mean (SD))	Correlation with Number Line Tasks
Number Skills	Arithmetic[1] (% correct)	85.6 (18.1)	r = 0.81, p = .004
	Subtraction (% correct)	85.0 (19.0)	r = 0.55, p = .09
	Multiplication (% correct)	86.0 (18.0)	r = 0.50, p = .13
	Dot Comparison (% correct)	77.5 (14.6)	r = 0.50, p = .14
	Counting Dots (% correct)	82.0 (18.7)	r = 0.90, p < .001
Visual-Spatial Skills	Dot Spatial Localization (max distance = 280 mm)	182.6 (39.4)	r = −0.21, p = .65
	Letter Cancellation Test (% correct)	79.3 (17.5)	r = 0.50, p = .17

NOTE

[1]Arithmetic is an average of the mean performance of subtraction and multiplication

TABLE 5

Corticobasal syndrome atrophy relative to control subjects

Peak Anatomic Locus (Brodmann Area)	Coordinates			Z-score
	X	Y	Z	
CBS < CONTROL				
R. intraparietal sulcus (7)	32	−68	46	3.97
R. inferior parietal (40)	46	−46	56	4.21
R. prefrontal (10)	16	58	−12	4.63
R. inferior frontal (44)	53	3	15	5.32
R. inferior frontal (47)	42	19	−14	4.92
R. superior temporal (22)	57	−32	13	5.36
R. amygdala	20	−1	−17	4.40
R. medial occipital (19)	16	−58	−1	5.84
R. medial occipital (18)	16	−79	15	4.33
L. intraparietal sulcus (7)	−20	−59	32	5.56
L. inferior frontal (47)	−38	28	−17	4.03
L. medial frontal (10)	−12	60	−1	4.85
L. insula	−40	−29	−5	5.17
L. superior temporal (22)	−60	−23	3	4.13
L. occipital (19)	−50	−72	7	4.95

APPENDIX

ARABIC NUMERAL STIMULI

Bounding Number 1	Bounding Number 2	Target number probed
2	4	3
11	14	13
3	4	2
7	3	5
19	14	16
14	11	13
9	7	5
18	11	13
4	6	2
17	15	16
4	7	5
19	16	12
19	15	17
3	8	6
15	17	13
6	8	3
18	12	15
2	9	5
19	18	16
5	7	6
17	14	15
4	6	2
5	9	7
18	13	15
17	15	12
9	6	3
12	19	14
16	19	12
12	14	13
9	6	8
16	17	15
5	7	4
9	4	7
17	15	13
13	19	16
8	1	6
6	8	3
19	17	18
1	4	3
17	14	11

ARABIC NUMERAL STIMULI		
Bounding Number 1	**Bounding Number 2**	**Target number probed**
13	17	15
7	2	4
4	8	1
14	13	12
8	1	4
9	8	6
9	7	8
16	19	18
16	19	13
7	4	2
6	2	4
12	17	15
14	16	12
9	3	6
5	9	2
12	16	14
1	7	4
12	19	16
7	5	2
11	17	14
8	2	5
9	7	5
4	6	5
6	5	3
5	6	4
5	9	7
8	3	5
18	17	15
9	3	7
5	7	3
8	1	5
15	18	13
16	18	17
15	13	14
15	17	11
19	14	12
5	8	7
5	8	1
2	7	5
5	7	1
1	8	5

ARABIC NUMERAL STIMULI		
Bounding Number 1	**Bounding Number 2**	**Target number probed**
18	17	16
7	1	5
3	9	7
7	8	5
17	15	13
8	5	7
7	3	5
9	2	4
15	17	11
3	8	5
9	4	2
7	2	5
8	7	6
2	9	4
17	15	12
8	6	7
3	6	5
7	8	5
3	7	5
DOT ARRAY STIMULI		
Bounding Number 1	**Bounding Number 2**	**Target number probed**
4	2	3
4	7	5
5	9	7
6	8	1
3	8	6
8	2	5
8	5	2
1	8	6
9	6	8
8	6	3
5	7	3
6	2	4
4	9	7
9	8	6
9	3	6
4	3	2
5	9	2
2	7	4
5	7	6
4	7	1

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ARABIC NUMERAL STIMULI		
Bounding Number 1	**Bounding Number 2**	**Target number probed**
9	6	8
7	3	5
9	7	4
2	9	5
1	7	4
6	4	2
8	1	4
3	4	1
1	4	3
6	7	5
1	3	2
3	6	5
6	8	4
5	1	3
4	5	2
7	2	4
8	4	6
5	8	2
9	3	6
8	5	1
8	6	7
1	8	4
6	5	3
1	6	4
2	8	5
9	6	3
9	2	5
5	2	4
4	6	1
1	8	6
5	4	3
6	4	2
5	8	7
7	4	2
3	5	4
8	7	6
1	7	4
5	9	7
5	9	2
9	4	7