Selective Interference with the Representation of Size in the Human by Direct Cortical Electrical Stimulation

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Abstract

■ A specific category in human cognition, size representation, was disrupted by the application of cortical electrical interference through a recently modified technique involving implantation of indwelling subdural electrode arrays. When subjected to electrical stimulation at a specific site, the subject was unable to access size information when questioned verbally, but showed no deficit if the size discrimination was presented visually. Verbal questions about size were answered correctly when the patient was not subjected to cortical interference. Other measures of verbal and visual comprehension for the categories of color, shape, orientation, movement, texture, and structure, tested under cortical interference, were normal. This clear-cut distinction between verbal and visual access to information about size, shown by a reversible block at a known and anatomically circumscribed site, provides further evidence that higher order neural processing is categorically represented. ■

INTRODUCTION

Processing of information in the human brain is thought to occur in a categorical fashion, but the neural bases for such processing are still obscure (Damasio, 1990). Cerebral injury has been reported to result in selective impairment in the processing of specific categories including animate objects, animals, fruits and vegetables, plants, body parts, inanimate objects, indoor objects, colors, and proper names (see Nielsen, 1936; Warrington & McCarthy, 1983; Warrington & Shallice, 1984; Hart, Berndt, & Caramazza, 1985; Humphreys & Riddoch, 1987; Damasio, 1990, for review). Such results have been considered significant, not only because they reveal a categorical structure of knowledge representation, but also because they appear to show that categorical representations are specifically organized within neuroanatomic structures. However, the significance of such studies has been questioned because of several fundamental limitations. First, these deficits have developed from accidental and essentially permanent lesions, such as cerebrovascular ischemia or degeneration, and it has not been possible to determine the individual's abilities before the lesion occurred. Therefore, it has never been certain that the impaired performance was actually caused by the lesion. The possibility exists that the impairment represents merely an idiosyncratic feature of that individual's normal mental state or that it was a behavioral state resulting from the recovery process. Second, because the lesions usually have been large and poorly defined, precise neuroanatomic correlation with cognitive dysfunction has rarely been possible.

We present a unique category-specific impairment, one that creates a new class of categorical neural distinctions, which is noteworthy for two additional reasons. First, it affected only verbal access to visual size information, indicating that the categories of human information can be very restricted and not predictable from prior scientific knowledge. Second, these data were obtained with a small, circumscribed "functional lesion." This "lesion" was temporary, as a result of electrical current being applied directly to a patient's cortex through an indwelling electrode array (Lesser, Lueders, Klem, Dinner, Morris, Hahn, & Wyllie, 1987), rather than from an essentially permanent lesion due to a cerebrovascular or other cerebral accident. Our study, with its within-subject design using reversible cortical interference, was not subject to the possible limitations of the studies mentioned above. Therefore, we were able to establish rigorously that the current caused a specific impairment compared to an individual patient's normal abilities. We were also able, in this case, to identify precisely the location of the responsible electrodes with respect to the brain regions that are likely involved in size processing.

RESULTS

The only impairment evident from the results of the experimental tasks was a deficit in verbal size judgment for objects under electrical stimulation that was not present without stimulation (see Table 1). The patient's performance was at chance for both size judgments using the terms "bigger" (chance performance, binomial $p = 0.85$) and "smaller" (chance performance, binomial $p = 0.51$). Additional testing (Table 1) showed that this impairment was not due to disruption of any of the basic language functions required to perform this task. Auditory comprehension in general, repetition of the size comparison questions, understanding of the terms comparing size ("bigger" or "smaller"), ability to name the objects under study, and verbal size comparisons involving numbers were all normal during stimulation at the same electrode pair.

No deficits were noted in visual perception or in the patient's ability to compare sizes visually during stimulation at the critical site. This was true for pairs of circles, squares, and other geometric shapes (two different-size shapes were presented and the question was, "Which one is bigger?"). The patient's performance was intact when comparing pairs of objects and animals presented visually in photographs and in line drawings scaled so that the depictions were of identical physical size (in which case the question was, "Which one of these objects is bigger in the real world?"). In general, the objects and pictures represented were the same as had been used in verbal size testing. Even with the same objects and pictures used in the verbal size testing, no deficits were noted for visual size comparisons in which line drawings were scaled so that the depictions were of identical physical size.

Verbal access to information other than that involving size was not affected. Knowledge of color, shape, texture (soft/hard? rough/smooth?), orientation (right side up?), movability (self-propelling?), or structure (part of an object? bend?) was normal on verbal testing even with electrical cortical interference at the critical site, and even for those items that the subject was unable to compare verbally with respect to size (see Table 1).

There was no effect of the magnitude of the difference in size between the objects being compared (Paivio, 1971, 1975; Foltz, Poltrock, & Potts, 1984): She was 3/14 correct for comparisons involving large differences in size (e.g., mouse–elephant) and 3/11 correct for comparisons involving small differences in size (e.g., apple–lemon) (χ^2 of homogeneity $= 0.017, p > 0.05$).

The subject's performance on the size comparison task was not affected by the possible existence of verbal labels (Smith & Medin, 1981) for the size of some of the items (that is, by the subject's possible verbal knowledge that "an ant is *small*" or that "an elephant is *large*"). On a post hoc analysis, items that had been presented were divided into those felt more likely to have verbal labels for their size in the subject's language system (e.g., ants and elephants) and those not likely to have such labels (e.g., cat). Whether the magnitude of the difference between the comparisons of the size labels had an influence was also examined as well. Neither variable proved to have an effect: She was 1/5 correct when two items with similar size labels were compared [e.g., two "big" labeled items]; 0/4 correct when two items could have labels indicating different sizes [e.g., one "big," one "small"]; 8/21 correct when one item could be labeled for size and one could not; and 4/11 correct when there could be no labels for either item (χ^2 of homogeneity $= 3.16, p > 0.05$).

DISCUSSION

Cortical stimulation at one particular point in this subject produced a selective defect in her ability to access size information verbally, but not visually. Stimulation at this site did not produce deficits in other cognitive functions that might be involved in these abilities; her auditory perception and comprehension were intact, as was her ability to make size comparisons of numbers.

We interpret these results as evidence that in this subject, verbal size comparisons were (1) normally accomplished by accessing visually based information, and that (2) the main effect of the cortical stimulation was to block this access from the verbal to the visual domains, but (3) in a selective manner, affecting only size information, and not blocking access to other types of visually based information. Her ability to make verbal comparisons of number size (magnitude) reflects the fact that number size is directly encoded in the stimulus, and does not require any reference to visual information. However, verbal comparison of the size of two items such as "apple" and "lemon" requires such access to visual information (Paivio, 1971; Moyer, 1973; Paivio, 1975; Kosslyn, Murphy, Bemesderfer, & Feinstein, 1977; Holyoak, 1977; Moyer, Bradley, Sorensen, Whiting, & Mansfield, 1978; teLinde, 1982; Foltz, Poltrock, & Potts, 1984), since the relevant information is neither directly encoded in the stimulus (as with numbers), nor would it be available from a verbal tag. Since her ability to do the verbal size comparison task was impaired by the stimulation, that deficit and her pattern of preserved functions implies that it was this access to visual information that was being selectively blocked. The subject also did have a profound impairment making verbal size comparisons when the items *might* have had verbal size labels (e.g., elephant) (Smith & Medin, 1981). This suggests that either such verbal/linguistic associations were not part of her particular prior knowledge in general, or that the strategy she adopted for the task did not use them, or that these

Table 1. Experiments on Size Judgment and Other Relevant Functions at the Site

		Without interference	*With interference*
1. Comprehension/Identification Functions			
Verbal definitions of "bigger" and "smaller"	Correct	2	2
(Verbally providing the meaning of each term)	Incorrect and "don't know"	0	0
Gestural demonstrations of "bigger" and "smaller"	Correct	2	2
(Visually showing by gestures the meaning of each term)	Incorrect and "don't know"	0	0
Visual confrontation naming	Correct	52	50
(Naming of photos of stimuli from the verbal size	Incorrect	0	0
judgments task)	"Don't know"	0	2
2. Auditory-Verbal Short-Term Memory Functions			
Repetition (words from verbal object/animal size	Correct	80	80
judgments)	Incorrect and "don't know"	0	0
Repetition (sentences from verbal object/animal size	Correct	10	10
judgments)	Incorrect and "don't know"	0	0
3. Object/Animal Size Judgments			
Verbal presentation			
Verbal size judgment—"bigger"—(objects)	Correct	37	15[a]
(e.g., "Is a tree bigger than an ant?")	Incorrect	0	13
	"Don't know"	0	15
Verbal size judgment—"smaller"—(objects)	Correct	26	21[b]
(e.g., "Is a bee smaller than a house?")	Incorrect	0	16
	"Don't know"	0	6
Visual presentation			
Visual size judgment (object photos)	Correct	20	20
(e.g., Present a photo of an elephant and a photo of a dog and ask, "Which one is bigger in real life?")	Incorrect and "don't know"	0	0
Visual size judgment (size-matched object drawings)	Correct	30	30
(e.g., Present an elephant and a bike scaled to the same size and ask, "Which one is bigger in real life?")	Incorrect and "don't know"	0	0
4. Nonobject Size Judgments			
Verbal size judgment (numbers)	Correct	17	20
(e.g., "Is 56 bigger than 42?")	Incorrect	1	2
	"Don't know"	0	0
5. Other Property Judgments			
Verbal presentation			
Verbal texture judgment (objects)	Correct	10	10
(e.g., "Is sandpaper rough/smooth?")	Incorrect and "don't know"	0	0
Verbal movement judgment (objects)	Correct	9	9
(e.g., "Can a mountain move/not move?")	Incorrect and "don't know"	0	0
Verbal orientation judgment (objects)	Correct	5	5
(e.g., "Does a car have a right-side up/only one correct position at rest?")	Incorrect and "don't know"	0	0
Verbal structure judgment (objects)	Correct	12	12
(e.g., "Does a pencil bend?")	Incorrect and "don't know"	0	0
Verbal-to-visual presentation			
Orientation judgment (object drawings)	Correct	26	20
(e.g., Present a line drawing of a car positioned upside-down and ask, "Is this object right side up/correct	Incorrect	1	1
position?")	"Don't know"	0	0
Color and shape judgments (Token Test—	Correct	85[c]	8
De Renzi & Vignolo, 1962)	Incorrect and "don't know"	0	0

[a] Chance performance, binomial $p = 0.85$.

[b] Chance performance, binomial $p = 0.51$.

[c] Note that this is the sum of all nonstimulated trials at all electrode sites, not just this site, for this task.

associations were suppressed by the stimulation as well. Regardless, the critical finding remains that a task requiring access to visual information from the verbal system could be selectively dissociated from other impairments of verbal or visual processing in the human.

More importantly, these data also demonstrate that the disruption in the verbal-to-visual connection can affect only a single category of knowledge (or subset of categories), and leave the connections for other types of knowledge, and the processing of other types of knowledge, completely intact. The other categories in our case were chosen for testing because studies of either nonhuman primates or human pathology suggest that these categories have distinct processing channels (Semmes, Weinstein, Ghent, & Teuber, 1960; Ridley & Ettlinger, 1976; Mishkin, 1979; Zeki, 1980; Livingstone & Hubel, 1984, 1988a, 1988b; Van Essen, 1985; Burkhalter & Van Essen, 1986; Braddick, Wattam-Bell, & Atkinson, 1986; Biederman, 1987; Poggio, Gamble, & Little, 1988; Lueck, Zeki, Friston, Deiber, Cope, Cunningham, Lammertsma, Kennard, & Frackowiak, 1989). Although we cannot be certain that size was the only category affected in this patient, it is clear that the other categories tested were intact, implying that even if all possible categories could have been tested, only a small subset would have been affected.

The category, size, found to be impaired in the present study is an inferred physical property. In this respect, the nature of the impairment in this subject differs from those previously described, which has been in purely perceptual (e.g., color) or in abstract semantic categories (e.g., fruits and vegetables). This case thus extends the classes of categorical cognitive distinctions that appear to be respected by neural processing mechanisms in humans. Moreover, this study, which was performed in a controlled setting under conditions where baseline performance of tasks could be rigorously compared to performance during stimulation, lends validity to observations of such types of dissociations seen in persons with more permanent cerebral lesions, whose condition does not permit such comparison with their premorbid state.

The types of deficits found from acquired lesions had perhaps been difficult to accept, because they suggested such a nonintuitive organization of the responsible cognitive functions and neural structures. The verbal size comparison deficit found in our subject from electrical stimulation, and the one recently described in visual size discrimination in rhesus monkeys produced by focal ablation (Schiller & Lee, 1991), imply that not only is such nonintuitive organization genuine, but it is likely to be pervasive.

The anatomical site where the electrical interference was applied in our subject also appears to be significant. The current was applied at a precisely known location in the posterior portion of the middle temporal gyrus of the dominant (left) hemisphere, 6.0–7.0 cm posterior to the temporal tip (see Fig. 1). In this location, current might have disrupted communication or integrative processes between the regions in the superior temporal gyrus where primary input of language occurs [based on standard cerebral processing anatomy of language (Mazzocchi & Vignolo, 1979; Selnes, Knopman, Niccum, Rubens, & Larson, 1983; Knopman, Selnes, & Rubens, 1989) and confirmed in our patient by cortical stimulation mapping] and the inferior temporal region(s), which has been shown to be important in the higher stages of processing of visual information and object recognition in both nonhuman primates (Ungerleider, 1985; Mishkin, 1990) and humans (Farah, 1984; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Goldenberg, Podreka, Steiner, Willmes, Suess, & Deecke, 1989; Petersen, Fox, Snyder, & Raichle, 1990; Haxby, Grady, Horwitz, Ungerleider, Mishkin, Carson, Herscovitch, Schapiro, & Rapoport, 1991).

METHOD

Subject

The subject was a 39-year-old college graduate who had had medically intractable epilepsy of left temporal lobe origin since age 19. This was associated with a small, intraparenchymal angioma in the medial aspect of the left inferior temporal region, approximately 3.5 cm posterior to the temporal tip. We had previously established that baseline neuropsychological function in this subject was essentially normal except for mildly impaired frontal lobe-type function (Heaton, 1981), mild dysnomia on visual confrontation testing (Goodglass, Kaplan, & Weintraub, 1983), and slight dyscalculia. Left cerebral dominance for language was determined by intracarotid

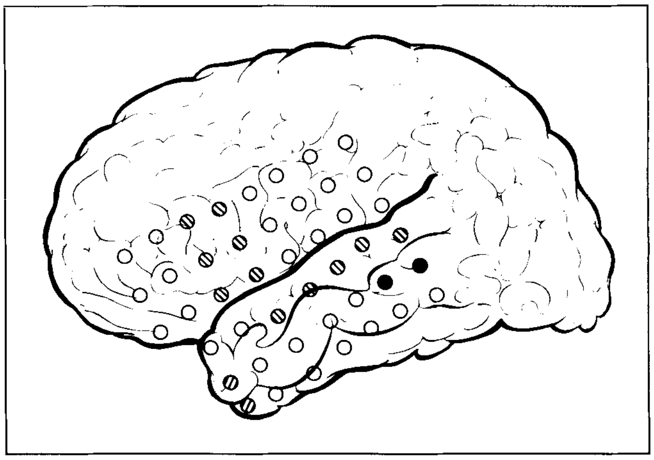

Figure 1. Scale drawing of left cerebral hemisphere and electrode locations. The black-filled circles indicate the pair of electrodes giving rise to the deficit in verbal size comparison. Open circles indicate electrodes not associated with language functions and lined circles indicate sites at which current impaired primary language functions by use of a standardized battery (Lesser et al., 1987; Gordon, Lesser, Hart, Selnes, Uematsu, 1989).

amobarbital testing (Wada & Rasmussen, 1960; Milner, 1975; Hart, Lesser, Fisher, Schwerdt, Bryan, & Gordon, 1991).

Procedure

As part of her surgical treatment for epilepsy, indwelling subdural arrays were surgically placed on the surface of the cortex for ictal and interictal recording and for cortical interference mapping (Lesser, Lueders, Klem, Dinner, Morris, Hahn, & Wyllie, 1987; Uematsu, Lesser, Fisher, Krauss, Hart, Vining, Freeman, & Gordon, 1990). These arrays were left in place, while the patient was ambulatory, for 12 days, in accord with standard clinical procedure (Lesser, Lueders, Klem, Dinner, Morris, Hahn, & Wyllie, 1987; Lueders, Lesser, Dinner, Morris, Hahn, Friedman, Skipper, Wyllie, & Friedman, 1987). This allowed prolonged testing with electrical stimulation in comfort and safety (Gordon, Lesser, Rance, Hart, Webber, Uematsu, & Fisher, 1990). The subject gave full informed consent for both the clinical and the research procedures described here, as approved by our institution's Human Subjects Committee.

Conditions for electrical stimulation (Lesser, Lueders, Klem, Dinner, Morris, & Hahn, 1984; Lesser, Lueders, Klem, Dinner, Morris, & Hahn, 1985) and testing procedures at each electrode (Gordon, Lesser, Hart, Selnes, & Uematsu, 1989) were as follows. Arrays of electrodes embedded in silastic were implanted subdurally through craniotomy (Lesser, Lueders, Klem, Dinner, Morris, Hahn, & Wyllie, 1987). Electrodes consisted of 90% platinum–10% iridium flat discs, embedded in Dow Co. medical-grade silastic with 2 mm exposed, recessed approximately 0.1 mm below the plane of the surface. Electrodes were placed 10 mm center-to-center, in arrays (Wyler-type, Ad Tech Medical Instrument Corp., Racine, WI), externally connected through a multiminicable system. In this patient, based on the preoperative evaluation (Lesser, Lueders, Klem, Dinner, Morris, Hahn, & Wyllie, 1987), one 2 × 8 array was placed over the anterior and inferior-basal temporal lobe, and another 6 × 8 array was placed over the left perisylvian region, and oriented so that its inferior rows of electrodes were approximately parallel to, and overlying, the lateral temporal gyri.

Electrode positions were determined independently by direct visual inspection at the time of operative placement and removal, as well as by photographs taken at the same time, by plain skull X-rays, and by overlay of X-ray computed tomographic (XCT) images of the implanted arrays onto preoperative magnetic resonance imaging (MRI) scans. The XCT was done on a Siemens Somatom DR3 scanner (Siemens Medical Systems Inc., Islin, NJ), with 4-mm slice thickness, 3-mm table incrementation, 0° gantry angulation, 450 mA/sec, 125 kVp, and a high-resolution convolutional filter. The MRI was obtained on a General Electric 1.5 T machine, with slice thicknesses of 5 mm. One scan was done with TR = 3333 msec, TE = 30 msec; the other, TR = 3333, TE = 100. Superimposition was performed on a Loats Image Analysis System (Loats Associates, Westminster, MD). All methods agreed on the localization of all the electrodes of interest.

Electrical stimulation was done with a Grass SU88 stimulator with dual Grass SIU7 optical isolation units (Grass Instrument Co., Quincy, MA). Stimulation pulses were square waves of 0.3 msec duration, of alternating polarity, at 50 pulses per second. At each electrode pair, a maximal current for testing was determined by either (1) the machine maximum (15 mA), (2) limits set by the production of afterdischarges, or (rarely) (3) pain from stimulation of branches of the trigeminal nerve which may accompany the pia-arachnoid vasculature (Lesser, Lueders, Klem, Dinner, Morris, & Hahn, 1985). Current applied to the cortex in this manner appears to produce a temporary, localized interference with function, due to a massive depolarization of the underlying cortex and stimulation of intracortical and subcortical axons (Li & Chou, 1962; Landau, Bishop, & Clare, 1965).

The subject was tested while comfortable and fully alert, in her hospital room. Testing was carried out for several hours at a time, over several sessions. Adjacent pairs of electrodes were tested. At each pair, testing began at a low level of current, which was progressively increased. When the maximum current possible was reached (usually 15 mA, generally limited by the stimulation unit's capabilities, but sometimes by factors such as afterdischarges or pain), more extensive testing was then performed at each site: subjective reports, positive motor signs, ability to move the tongue, lips, face, hands, and feet, and then language testing. Language testing at almost all sites (including the electrode pair in question) included the following basic tests (Gordon, Lesser, Hart, Selnes, & Uematsu, 1989): auditory comprehension, assessed with a single-step, modified form of the Token test (Selnes, Niccum, Knopman, & Rubens, 1984), repetition of single words, production of spontaneous speech (from pretested topics of interest to the patient), visual confrontation naming, with use of line drawings from the Boston Naming Test (Goodglass, Kaplan, & Weintraub, 1983), naming to description, reading of single words, and reading of paragraphs. Items too difficult for or unknown to the subject were eliminated in pretesting. Visual materials were presented on single sheets about 12–15 inches in front of the patient. Materials for reading were printed in large letters. Stimuli were given one at a time when feasible. Trials with and without electrical interference were mixed semirandomly, with both the subject and the tester blinded to the application of the electrical stimulation. Electrical interference, which generally lasted 0.5–3 secs, was begun just before presentation of the language stimulus, and ended after the stimulus was removed, just before the response phase. Electrocortical activity was continually monitored through the indwelling subdural arrays, except during the immediate time when electrical interference was being applied (because stimulation artifact contaminated the recording, preventing visualization of electrocortical activity).

Results of all trials were recorded by hand, and also videotaped. Trials with possible interference (e.g., motor impairment, momentary lapse of attention, EEG evidence of seizure discharges, or afterdischarges) were discarded from the analyses. Trials were marked as incorrect if there was either inability to respond, or an erroneous response.

For the language tests in general, stimulated performance at a pair of electrodes was compared to nonstimulated performance, using a two-tailed binomial test. The task-wise Type I error rate for significance was set at $p < 0.05$.

Various language functions were found to be impaired as a result of this "functional lesion," at sites on the posterior frontal lobe [in the general region of the classical motor speech region(s)], the superior temporal lobe (the classical posterior language area), and in an anterior, inferior temporal region frequently associated with speech impairments with electrical stimulation (Burnstine, Lesser, Hart, Uematsu, Zinreich, Krauss, Fisher, Vining, & Gordon, 1990; Lueders, Lesser, Hahn, Dinner, Morris, Wyllie, & Godoy, 1991) (see Fig. 1).

During the initial language function testing, when cortical interference was applied at one electrode pair just inferior to the posterior language area, we noted that the patient was unable to compare the size of objects when asked verbally (e.g., "Is an apple bigger than a lemon?") (see Table 1). Consequently, with the patient's full consent, we undertook an extensive series of tests to evaluate this unexpected finding more completely.

This evaluation continued over 2 days and 3 testing sessions. The current used as 12–14 mA, limited in this patient, at this site, by the development of afterdischarges at higher current levels (Lesser, Lueders, Klem, Dinner, Morris, & Hahn, 1984). For each testing session, the presence of the basic size processing deficit at the new current level was reestablished, in keeping with the clinical testing paradigms (Lesser, Lueders, Klem, Dinner, Morris, & Hahn, 1984).

To more fully explore the size judgment impairment, we performed the following tasks using the same electrical interference testing protocol as described above:

1. Verbal size judgment for objects ("bigger" and "smaller")—Questions requiring size comparison of two objects (e.g., "Is a tree bigger than an ant?") were presented verbally to the patient for a yes–no response. At one testing the size comparison term used was "bigger," and at the next testing session, the comparison term used was "smaller." These questions ranged from disparately sized objects (e.g., tree–ant) to similarly sized objects (e.g., apples–lemons).
2. Visual size judgment for objects (object photos)—The patient was shown two photographs of objects and asked to point to the larger object in real life.
3. Visual size judgment for objects (size-matched object drawings)—The patient was shown two line drawings of objects that were scaled to the same size and asked to point to the larger object in real life.
4. Verbal size judgment (numbers)—Questions requiring number quantification comparison were presented verbally to the patient for a yes–no response (e.g., "Is 56 bigger than 42?").
5. Verbal property judgment for objects (texture, movement, orientation, structure)—Questions (requiring a yes/no answer) were presented to the patient regarding properties of objects (e.g., "Is sandpaper rough? Can a mountain move? Can a dog move on its own? Can a car move with fuel? Can a library be thrown? Does a car have a right side up? Can you bend a pencil? Do you have hair on your feet . . . on the soles of your feet?") The objects used were the same ones used for the verbal size judgment task, when possible.
6. Verbal-to-visual property judgment for objects (orientation, color, shape). While viewing an object visually, questions were asked verbally about a particular property of the object (e.g., a picture of a car was presented upside-down, sideways, or correctly oriented and the patient was asked, "Is this object right-side up?").

To ensure that the patient registered the verbal size judgment questions, the individual objects, and the comparison terms, we performed the following tests:

7. Comprehension of size comparison terms—The patient was asked to verbally define and gesturally demonstrate the meaning of the terms "bigger" and "smaller."
8. Visual confrontation naming of objects—Line drawings of all the objects used in this study were presented visually for the patient to name orally.
9. Auditory repetition of verbal size judgment questions—Questions were presented auditorily and the patient was asked to repeat each verbal size judgment question (Experiment 1), as well as each word of the question.

To ensure that this deficit was not purely a perceptual phenomena, we tested visual size comparison of geometric figures:

10. Two geometric figures (e.g., circles, squares) of different sizes were presented visually, and the subject was asked to point to the larger figure.

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