

Short-term and long-term verbal memory: A positron emission tomography study

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Communicated by Endel Tulving, University of California, Davis, CA, February 9, 1995 (received for review December 28, 1994)

ABSTRACT Short-term and long-term retention of experimentally presented words were compared in a sample of 33 healthy normal volunteers by the [¹⁵O]H₂O method with positron emission tomography (PET). The design included three conditions. For the long-term condition, subjects thoroughly studied 18 words 1 week before the PET study. For the short-term condition, subjects were shown another set of 18 words 60 sec before imaging, with instructions to remember them. For the baseline condition, subtracted from the two memory conditions, subjects read a third set of words that they had not previously seen in the experiment. Similar regions were activated in both short-term and long-term conditions: large right frontal areas, biparietal areas, and the left cerebellum. In addition, the short-term condition also activated a relatively large region in the left prefrontal region. These complex distributed circuits appear to represent the neural substrates for aspects of memory such as encoding, retrieval, and storage. They indicate that circuitry involved in episodic memory has much larger cortical and cerebellar components than has been emphasized in earlier lesion studies.

Human memory is a complex phenomenon that has been variously conceptualized by cognitive neuroscientists, on the basis of data from lesion studies, animal experiments, and *in vivo* microelectrode stimulation of the human brain (1–9). Strength and ease of memory encoding and retrieval appear to be linked to a variety of factors, such as novelty of the information, amount of practice, duration and frequency of exposure, depth of processing, or the origin of the information and the relationship of the individual to it (i.e., intrinsic vs. extrinsic, participant vs. nonparticipant) (6, 10–12). A fundamental question embedded in memory research is whether memory is a unitary construct. Since the original subdivision into primary and secondary by William James, models have been developed to classify it in various ways, invoking constructs such as procedural vs. declarative, implicit vs. explicit, episodic vs. semantic, working vs. reference, or short-term vs. long-term (3, 6, 10–21). Modern cognitive neuroscience seeks to link these models to their neural substrates. *In vivo* neuroimaging techniques such as positron emission tomography (PET) have provided a new approach to studying these models by permitting measurement of physiological activity while the brain is performing specific tasks (13–27). While lesion studies in animals and humans permit inferences about brain organization by indicating what fails to work when parts of the brain have been damaged, neuroimaging studies permit inferences based on measuring changes in metabolic activity during performance of tasks that can be experimentally controlled.

Here we report on a PET experiment designed to examine the neural substrates of recognition of previously learned verbal material. We compared long-term and short-term re-

tention of experimentally presented sets of common English words. The two conditions contrasted retrieval (recognition) of well-learned words, initially learned 1 week earlier, with retrieval (recognition) of a less well-learned list to which the subjects were exposed 60 sec prior to PET data acquisition. This study was influenced by lesion studies in animals and humans suggesting that bilateral injury to the medial temporal lobes produces an irreversible impairment in ability to remember new information for longer than a minute or two; such injury is thought to prevent the process of consolidation, which is considered to be a fundamental stage in the formation of long-term memory traces (5, 6, 8). We reasoned that consolidation might be more actively occurring, and that the medial temporal lobes would therefore be more actively engaged, during the short-term than during the long-term retention task. We anticipated that additional distributed portions of memory circuitry would also be identified in language and association cortex. In this report the terms long-term and short-term are purely descriptive; they designate the length of the retention interval used in the two tasks.

METHODS

Subjects. Subjects were 33 healthy normal volunteers recruited from the community by newspaper advertising. They were screened by structured interview techniques to rule out psychiatric, neurological, or serious medical illnesses. Twenty-one were female and 12 were male. Their mean age was 26.7 years (SD, 8.1), and their mean educational level was 14.5 years (SD, 1.6). All were right-handed. All gave written informed consent to a protocol approved by the University of Iowa Human Subjects Institutional Review Board.

Cognitive Tasks. The study included three conditions, which were chosen to permit comparisons across tasks: long-term retention, short-term retention, and reading words (experimental baseline). The major independent variable was the interval between learning the words and the recognition test of the words learned. For the condition referred to as long-term, 1 week prior to the PET study subjects were taught to recall a list of 18 words in a single training session. Subjects were given successive study-and-test trials in a free-recall task, with self-paced item presentation on a video monitor, until they reached the criterion of perfect performance; subjects took an average of three trials to reach this criterion. A second training session was provided on the day before the PET experiment; subjects were again asked to recall the 18 words; if they had any errors, they were reexposed until they had perfect recall; they were then given a single yes/no recognition test that included a set of distractor words. All subjects showed perfect recognition memory. For the condition referred to as short-term, subjects were instructed to remember a new list of 18 words; items were presented on a video monitor in a single trial one

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Abbreviations: MR, magnetic resonance; PET, positron emission tomography.

at a time at a rate of one item every 2 sec; the last item was shown to the subjects 60 sec before the yes/no recognition test was begun during the PET data acquisition. The experimental baseline consisted of reading aloud a new set of common English words of the same length and frequency as words used for the memory conditions. Another baseline, consisting of "resting" with eyes closed, was available for a subset of 14 subjects in this study. Since the awake brain is not inactive, however, this condition is probably better thought of as measuring the activity of the free-associating brain. The entire PET study included several other tasks/injections (involving facial recognition) that will be discussed in a separate publication.

Tasks were designed so that stimulation and output were as similar as possible across tasks during PET data acquisition. All words used in the study consisted of one- or two-syllable concrete nouns of comparable frequency of usage (28). All stimuli were presented visually on a video monitor for 500 msec at 2.5-sec intervals, and all output consisted of a spoken verbal response by the subject. During the memory conditions, subjects were asked to respond with a "yes" or "no" to indicate whether the word seen on the video monitor was one that they had learned. The distractors used to intermix with the learned words consisted of similar concrete nouns matched to the learned words for frequency of usage. Twenty-two distractors were intermixed with the 18 targets to produce a higher concentration of targets during the PET scan. Specifically, 80% of all the test items appearing during the 40-sec interval used for analysis (see below) were target words. Performance of subjects was monitored in order to ascertain how well the subjects remembered the words. The hit rates were 0.97 and 0.87, and the false-alarm rates were 0.01 and 0.03, respectively. The duration of the task was 120 sec for all conditions.

PET and Magnetic Resonance (MR) Data Acquisition. The PET data were acquired with a bolus injection of 75 mCi (1 mCi = 37 MBq) of [^{15}O]H $_2$ O in 5–7 ml of 0.9% NaCl, using a GE PC4096-plus 15-slice whole-body scanner. Arterial blood was sampled from a catheter placed in the right radial artery to obtain the input function needed for calculation of tissue perfusion (milliliters per minute per 100 g of tissue). Arterial blood sampling and imaging began at the time of injection ($t = 0$) and continued for 100 sec. The tracer was injected via a venous line in the left arm. The time from injection to bolus arrival in the brain was individually measured by delivering a 15-mCi bolus during an initial sham scan during which subjects read words aloud. Images were acquired in twenty 5-sec frames. Based on the time of bolus arrival in the brain, the eight frames reflecting the 40 sec after bolus arrival were selected and summed, and these data were used in subsequent image reconstruction and analysis. The summed image was reconstructed into 2-mm voxels in a 128 \times 128 matrix by using a Butterworth filter (order = 6, cutoff frequency = 0.35 Nyquist interval). Cerebral blood flow was calculated on a voxel-by-voxel basis by the autoradiographic method, using the blood curve (expressed in PET counts) and an assumed brain partition coefficient of 0.90 (29). Injections were repeated at \approx 15-min intervals.

MR scans were obtained for each subject with a T_1 -weighted three-dimensional SPGR sequence on a 1.5-T GE Signa scanner [echo time (T_E), 5 sec; repetition time (T_R), 24 sec; flip angle, 40°; number of excitations, 2; field of view, 26; matrix, 256 \times 192; slice thickness, 1.5 mm].

Image Analysis and Statistical Analysis. The quantitative PET blood flow images and MR images were analyzed with the locally developed software package BRAINS (Brain Research: Analysis of Images, Networks, and Systems) (30–33). The outline of the brain was identified on the MR images by a combination of edge detection and manual tracing. MR scans were volume-rendered; the anterior commissure–posterior commissure line was identified and used to realign the brains

of all subjects to a standard position and place each brain in standardized Talairach coordinate space (34). The outline of the brain in the PET image was automatically identified with an edge detection algorithm. The PET image for each individual was then fit to that individual's MR scan by means of a surface-fit algorithm (30, 31, 35). Each injection was checked for head movement and individually refit as needed. The MR images from the 33 individuals were averaged, so that the functional activity visualized by the PET studies could be localized on co-registered MR and PET images where the MR image represented the "average brain" of the subjects in this study (31, 33). The co-registered images were resampled and simultaneously visualized in all three orthogonal planes, thereby permitting three-dimensional checking of anatomical localization of activity with a higher level of accuracy and detail than is provided by the Talairach atlas alone (30–33).

Statistical analysis of the images was performed by an adaptation of the method of Worsley *et al.* (36). An 18-mm Hanning filter was applied to the PET images to eliminate residual anatomical variability. Images were resampled to 128 \times 128 \times 80 voxels with the Talairach atlas (34). A within-subject subtraction of relevant injections was then performed, followed by across-subject averaging of the subtraction images and computation of voxel-by-voxel t tests of the regional cerebral blood flow changes. Significant regions of activation were calculated on the t -map images by a technique that corrects for the large number of voxel-by-voxel t tests performed, the lack of independence between voxels, and the resolution of the processed PET images.

Subtractions were chosen to make comparisons across conditions. The experimental baseline, involving reading visually presented words aloud, included visual input, verbal output, and word recognition. The two memory conditions involved each of these three tasks plus the processes of recognition memory. The statistical analyses consisted of the following subtractions: long-term minus baseline, short-term minus baseline, and long-term minus short-term retention. The first two subtractions isolate the brain circuitry involved in longer-term vs. shorter-term retention. The subtraction of short-term and long-term indicates specific differences in the circuitry involved in these two conditions.

The analysis involved an exploratory search, using a search volume of 600 cm 3 which corresponds to 243 resolution elements (resels). Calculated resel dimensions on our scanner (based on a point-source phantom) are 11 \times 11 \times 5.6 mm (before filtering), producing an overall resel size of 2.47 cm 3 (after filtering). The method for determining significant change in this search volume was based on the use of the Euler characteristic and three-dimensional Gaussian random-field theory (36). A t value of 3.61 was considered to be statistically significant ($P < 0.0005$, one-tailed, uncorrected). We report only those peaks that contained >500 contiguous voxels exceeding this threshold. Data are reported in tables by showing the t value associated with each significant area (or "peak") and the location of the voxel with the highest value using Talairach coordinates, region names, and Brodmann area numbers. The names of anatomic regions in the tables are based on visual inspection of MR-registered images.

RESULTS AND DISCUSSION

The areas identified as significant in the long-term-minus-baseline subtraction are shown in Table 1. Positive peaks, representing areas of increased blood flow during long-term retention, are distributed throughout the cortex and the cerebellum. Four peaks are found in the right frontal regions, encompassing Brodmann areas 10, 9, 46, and 47. A single peak is also present in the left frontal region. Additional positive peaks are seen in right and left parietal regions, the precuneus, the left cerebellum, and the anterior cingulate gyrus. The

Table 1. Long-term retention minus reading words

t_{max}	Coordinates			Location*
	R/L	Ant/Post	Sup/Inf	
Positive activations				
6.68	26	48	-15	R Fr Med/10
5.34	37	12	39	R Fr Med/9
5.31	30	44	10	R Fr Med/46
5.84	35	19	-5	R Inf Fr/47
5.83	-25	53	-14	L Fr Med/10
8.99	42	-47	42	R parietal/40
8.57	-42	-55	42	L parietal/40
8.99	-10	-82	-25	L cerebellum
5.14	-1	23	35	Ant cingulate
6.25	-1	-71	41	Precuneus
Negative activations				
-6.67	54	-5	-17	R insula
-6.05	-50	-17	26	L insula
-5.55	12	-9	57	R Sup Fr/6
-5.98	-29	-13	42	L motor/4

R, right; L, left; Fr, frontal; Med, medial; Ant, anterior; Post, posterior; Sup, superior; Inf, inferior.

*Numbers refer to Brodmann's areas.

location of some of the peaks and their associated t maps, mapped on a MR scan that represents the "average brain" of these 33 subjects, are shown in Fig. 1 *Upper*. The peaks provide a statistically truncated view of the geography of the circuitry. The t -map images give a more descriptive picture of the regions activated. The activated regions seen in these images can be inferred to reflect the circuitry involved in long-term retention for a word list that has been well learned.

The areas of increased activity lend themselves to a variety of interpretations. One explanation is that the large right frontal region holds the image of the word while it initiates its retrieval. The remaining regions in the parietal lobes and the cerebellum represent the distributed "storage" systems being referenced. The referencing process probably involves semantic, visual, and temporal checks. The presence of activation only in the left cerebellum is noteworthy, in view of selective activity in the right frontal areas; tracts between the frontal lobes and the cerebellum connect contralateral hemispheres. The increased areas of activity in the anterior cingulate may reflect the attentional demands of the task.

The results of subtracting reading words from short-term retention are shown in Table 2. A visual display of some of the peaks, using the same location as in Fig. 1 *Upper*, is provided in Fig. 1 *Lower*. The areas of activation are very similar to those seen in the long-term condition, with one notable exception. The second-largest peak in this condition involves area 10 on the left side, a region which produced a single small peak during the long-term condition. Tulving *et al.* (18, 20) have suggested that hemispheric asymmetry may exist for encoding vs. retrieval processes. These findings are consistent with his hypothesis, in that the subjects may be actively involved in encoding during the short-term condition, when the encoding process was completed during the previous week for the long-term condition. They are also consistent with the recent report of Shallice *et al.* (21) on the neural substrates of encoding and retrieval. The single activation in right frontal regions is large (a 51.3 cm³ peak above the 3.61 significance threshold, compared with a total of 12 cm³ for four right frontal peaks seen for long-term retention); it represents the coalescence of the multiple smaller areas observed in Table 1.

To determine the differences between short-term and long-term retention, these two conditions were subtracted from one another. There were only three significant positive peaks and no significant negative peaks. The largest peak ($x, y, z = -31,$

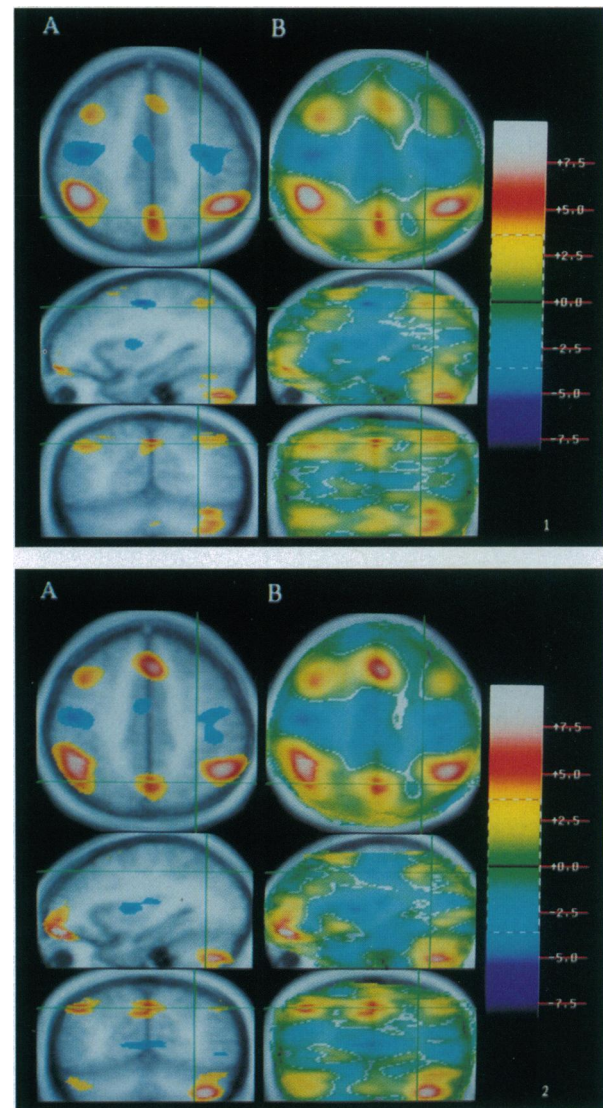


FIG. 1. (*Upper*) Side A shows peaks (areas of contiguous voxels that exceed the 3.61 significance threshold) for long-term retention minus reading words. Side B shows the t -map data. Three orthogonal planes of PET data registered on MR data are displayed to show positive (red/yellow tones) and negative (green/blue tones) t values in frontal, parietal, cerebellar, and temporal regions. Cross-hairs show the location of the images across the three planes. The numeric significance of the t value is shown on the color scale on the right side. Orientation is radiological (i.e., as if facing patient or viewing from foot of bed). (*Lower*) Sides A and B show peaks and t maps for short-term retention minus reading words. The pattern is strikingly similar to that seen for long-term retention, but the regions of activation are larger and more intense, reflecting the lack of previous practice. Although the frontal regions are not highlighted in this particular set of sections, the frontal area of activation is much larger. Sections in a more frontal plane (not shown) also indicate the presence of a prominent area of activation in the left hemisphere, which is only minimally present during the long-term condition.

45, -14) reflects the additional area of activation created by the encoding operations in area 10 of the left frontal lobe during short-term retention. A peak is also found more posteriorly in area 45 on the right ($x, y, z = 33, 14, 4$), perhaps reflecting the greater involvement of articulatory mechanisms during the remembrance of recently learned words. A peak is present in the anterior cingulate ($x, y, z = -2, 24, 29$), probably reflecting the greater attentional demands created by the short-term condition.

The subtraction of reading words from both short-term and long-term retention also produced large areas of negative

Table 2. Short-term retention minus reading words

t_{\max}	Coordinates			Location
	R/L	Ant/Post	Sup/Inf	
Positive activations				
10.43	27	48	-13	R Fr/9/10/47 extending to Ant cingulate/24
8.69	-27	49	-14	L Inf Fr/10
8.86	44	-47	45	R parietal/40
7.52	-43	-56	39	L parietal/40
7.99	-33	-69	-37	L cerebellum
5.97	-7	-82	-21	L Med cerebellum
6.10	-2	-69	39	Precuneus/7
Negative activations				
-6.22	52	-5	19	R insula
-7.57	-44	-2	5	L insula
-6.11	3	-16	45	Mid-cingulate/24
-5.01	7	-66	7	R Med Sup cerebellum
-5.88	-39	-39	-19	R Ant cerebellum

Abbreviations are as in Table 1.

activity in the superior temporal regions. Inspection of the registered images indicates that these are located above the superior temporal gyrus and the planum temporale and are located primarily in the insula and regions superior to it. Such bitemporal negativity has also been observed in other PET studies and has been variously interpreted (13–19, 22, 23). In two otherwise unrelated studies, Squire *et al.* (15) and Tulving *et al.* (18) have interpreted negativity arising from the subtraction of a “new” stimulus (reading a new list of words in the present experiment) from an “old” stimulus (recognizing a list of previously learned words in the present experiment) as reflecting the greater computational requirements for the recognition and identification of the new material; as such, they suggest that the negativity could mark the neural substrates of priming. Frith *et al.* (22, 23) have tentatively interpreted similar patterns, which occurred during tasks that require intrinsic (as opposed to extrinsic) generation of responses (i.e., verbal fluency or willed action tasks), as involving a strategic inhibition of these regions mediated by the prefrontal cortex. Grasby *et al.* (16, 17) have similarly interpreted their findings of bitemporal decreases during long-term (supraspan) memory tasks by using a graded response paradigm. Raichle *et al.* (13, 14) have suggested that the bitemporal decreases in flow may reflect processing using nonautomatic circuitry.

It is important, however, to determine whether the bitemporal decreases produced by the subtraction are due to deactivation occurring during the long-term retention task or whether they represent a relative bitemporal increase in the reading-words condition that is subtracted from the long-term condition. We explored this question by two different approaches. First, we measured absolute flow in the bitemporal regions during the long-term and the reading-words conditions. The results of this analysis are shown in Table 3. For purposes of comparison, absolute flow is also shown for frontal, parietal, and cerebellar regions. Flow in bitemporal regions is indeed higher during the reading words condition, but only minimally so, whereas it is substantially higher in frontal, parietal, and cerebellar regions during long-term retention. This suggests that the bitemporal negativity during long-term retention is not produced through greater temporal activity during reading words. Second, we subtracted the resting baseline from reading words. No significant peaks were found in the temporal regions, again suggesting that temporal activation during reading words is not the source of the negativity in the bitemporal regions during long-term reten-

Table 3. Average blood flow in specific brain regions during long-term retention and reading words

Region	Blood flow, ml·min ⁻¹ ·g ⁻¹ (mean ± SD)	
	Long-term retention	Reading words
Right frontal	66.6 ± 19.2	56.6 ± 15.5
Left frontal	65.0 ± 19.1	53.8 ± 15.1
Right temporal	62.6 ± 9.9	65.3 ± 12.1
Left temporal	64.2 ± 12.0	66.8 ± 12.1
Right parietal	86.0 ± 23.2	70.2 ± 15.1
Left parietal	86.8 ± 17.1	71.2 ± 12.1
Left cerebellum	82.0 ± 13.0	70.4 ± 12.1

Values represent the value in the voxel identified by the coordinates in Table 1.

tion. Taken together, these two analyses may suggest that the areas of bitemporal negativity could represent deactivation of temporal regions during the long-term condition.

IMPLICATIONS AND CONCLUSIONS

These results illustrate the difficulties that arise when one attempts to extrapolate findings from lesion studies in animals or humans to the investigation of metabolic activity in the intact brain during *in vivo* real-time processing. Because of the crucial role that the medial temporal lobes have been observed to play in the consolidation of memory in lesion studies, as well as the identification of activity there in some early PET studies (1, 5–7, 15, 16), we anticipated that either or both of the memory tasks would elicit medial temporal lobe activation. This did not occur. No significant activation was seen in the statistical maps, and an inspection of the co-registered individual MR and PET images confirmed that this area was inactive. Further confirmation for the absence of medial temporal activity was provided through the measurement of absolute regional cerebral blood flow (mean flow = 49.7 ml·min⁻¹·g⁻¹ for right hippocampus and 55.3 ml·min⁻¹·g⁻¹ for left hippocampus), which was the lowest measured region-of-interest during the long-term retention condition. These results do not disconfirm the role of the medial temporal lobes in consolidation, but they do suggest that the role may be relatively brief and that it was not captured in the particular time windows and paradigms employed in this PET experiment.

The areas activated in the short-term and long-term conditions were very similar, in spite of the fact that the tasks involved a substantial time difference in the delay between acquisition and testing during the PET experiment. Both tasks activated a distributed circuit that included the right frontal lobe, biparietal regions, and the left cerebellum. This suggests that memory for word lists learned 1 min earlier employs circuitry that is widely distributed and is similar to that involved in a well-practiced memory task. These results raise the possibility that the brain may contain “general memory circuitry” that is involved in tasks that tap episodic memory.

Within the context of the “components” of memory, the most likely explanation for the specific pattern of activation is that we are observing the substrates of encoding and retrieval, both occurring within the context of episodic memory. Both the short-term and long-term tasks require retrieval, which accounts for the similarity in pattern across these two conditions. The major difference is that the short-term task also is stimulating an active encoding process, which is visualized in the left frontal region. These results are consistent with the HERA model of Tulving and coworkers (18–20) that hemispheric asymmetry may occur for processes involving encoding and retrieval of episodic memory and that episodic memory may be involved even in tasks that on the surface might seem semantic in nature.

This experiment also compares a well-practiced or automatic task and a “nonautomatic” task that involves learning words 1 min prior to PET data acquisition. Its results are consistent with William James’ speculation that practice may permit the brain to work more efficiently (10); they are similar to the findings of Raichle and others (13, 14), who have shown that practice tends to reduce the areas activated, since automatic processing occurs more efficiently. The short-term retention task produced much larger areas of activation for most conditions, particularly in the right frontal lobe.

However these results are interpreted, they suggest the need for a critical reappraisal of our thinking about the neural substrates of human memory. The circuitry is surprisingly similar for both short-term and long-term conditions. It manages to function without involving the medial temporal lobes, considered to be a crucial component in consolidation. It includes regions not often thought to be involved in cognitive aspects of memory, such as the cerebellum. The cerebellum plays a major role in both the long-term and the short-term condition, to an extent that is clearly apart from procedural or automatic aspects of memory; it appears to function as a cognitive organ in the brain. The relationship between the memory processes examined in our two tasks and the neural processes in the *in vivo* human brain is clearly more complicated than previously believed: the neural circuitry of human memory is cortical, distributed, and complex.

This research was supported in part by National Institute of Mental Health Grants MH31593, MH40856, and MHCRC43271; The Nellie Ball Trust Fund, Iowa State Bank and Trust Company, Trustee; a Research Scientist Award, MH00625; and a National Association for Research on Schizophrenia and Affective Disorders Senior Investigator Award.

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