

Neurodevelopmental Aspects of Spatial Navigation: A Virtual Reality fMRI Study¹

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Received July 16, 2001

Navigation in spatial contexts has been studied in diverse species, yielding insights into underlying neural mechanisms and their phylogenetic progression. Spatial navigation in humans is marked by age-related changes that may carry important implications for understanding cortical development. The emergence of “allocentric” processing, reflecting that ability to use viewer-independent spatial abstractions, represents an important developmental change. We used fMRI to map brain regions engaged during memory-guided navigation in a virtual reality environment in adolescents and adults. Blood oxygen level-dependent (BOLD) signal was monitored in eight adolescents and eight adults in a 1.5-T MRI scanner during three conditions: (1) memory-guided navigation (NAV); (2) arrow-guided navigation (ARROW); and (3) fixation (FIX). We quantified navigation ability during scanning and allocentric memory after scanning, based on subjects’ ability to label a previously unseen, aerial view of the town. Adolescents and adults exhibited similar memory-guided navigation ability, but adults exhibited superior allocentric memory ability. Memory-guided navigation ability during scanning correlated with BOLD change between NAV/ARROWS in various regions, including a right frontal and right-anterior medial temporal lobe region. Age group and allocentric memory together explained significant variance in BOLD change in temporoparietal association cortex and the cerebellum, particularly in the left hemisphere. Consistent with developmental models, these findings relate maturation in the coding of spatial information to functional changes in a distributed, left-lateralized neural network. © 2002 Elsevier Science

Key Words: navigation; development; adolescence; neuroscience; fMRI.

INTRODUCTION

Recent cognitive neuroscience studies delineate neural circuits engaged by various mnemonic processes. Considerable basic knowledge in this area derives from studies in rodents employing spatial navigation paradigms with parallels in human research (Burgess *et al.*, 1999; Spiers *et al.*, 2001). Psychological studies document developmental changes in memory system function, stimulating interest in the relationship between psychological and neural development (Cycowicz *et al.*, 2000; Nelson *et al.*, 2000). Research on spatial navigation may provide insights on the precise nature of such relationships (Mayford and Kandel, 1999; Squire and Kandel, 1999; Silva *et al.*, 1998).

From the cognitive developmental perspective, pre-adolescent children tend to perform as well as adults when directly navigating in a novel environment (Cohen and Scheupfer, 1980; Overman *et al.*, 1996). However, other aspects of navigation mature relatively late in adolescence. This includes the ability to navigate efficiently by using abstract mental representations of the environment (Mathews, 1992). Directly navigating within an environment leads an individual to develop a mental representation that references location in the environment with respect to aspects of the external world, independent of individual body space. The term “allocentric representation” has been used to describe such “world-centered” representations, as contrasted with “egocentric” representations that reference spatial locations in the external world with respect to individual body space (Spiers *et al.*, 2001). Adults display greater efficiency than adolescents in using “allocentric representations” during navigation. Such de-

¹ This research was supported by NIMH Scientist Development Award for Clinicians to D.S.P. (MH-01391) and NIMH Center Grant MH-43878 to The Center to Study Youth Depression, Anxiety and Suicide at New York State Psychiatric Institute. We acknowledge the invaluable assistance from Bradley S. Peterson and Joseph Helfern in the conceptualization of the study.

velopmental differences are manifest as superior ability when navigating in novel environments using two-dimensional display of allocentric space, in the form of maps (Denckla *et al.*, 1980; Mathews, 1992; Silverman and Eals, 1992).

Changes in the ability to navigate efficiently by extrapolating from an allocentric representation to a real-world environment parallel broader cognitive changes that occur during adolescence. Descriptive representations of various constructs beyond maps of the environment become increasingly complex during this developmental stage. These include representations of emotional experiences or linguistic categories (Keating, 1990; Stattin, 1984). Moreover, the capacity of an individual to deploy such increasingly complex descriptive systems in memory retrieval and novel problem solving tasks also matures during adolescence (Fuster, 1997; Keating and Sasse, 1996). Such developmental changes allow mature individuals to efficiently transpose abstract representations in the service of problem solving activities, such as memory retrieval. These broad developmental changes are thought to reflect multiple aspects of adolescent brain development, and this capacity to utilize emergent descriptive systems for spatial processing is seen as particularly characteristic of cognitive processes mediated by left temporoparietal association cortex (Goldberg, 1989; Goldberg and Costa, 1981).

Brain development from childhood through adolescence is thought to involve changes within cortical association areas, particularly aspects of frontal, postrolandic temporoparietal, and medial temporal cortices (Lipska *et al.*, 1998; McGlashan and Hoffman, 2000; Mesulam, 2000). At a cognitive level, maturation within these brain regions is thought to facilitate processes that require extrapolation of descriptive schemes across contexts (Carey and Diamond, 1980; Goldberg, 1989). Because map-guided navigation provides a salient example of such processes, research on navigation may delineate neural and psychological processes that show parallel changes across developmental periods. At a neural circuitry level, spatial navigation paradigms have been used to delineate brain regions engaged during memory retrieval, including components of the temporal and frontal lobes (Kahana *et al.*, 1999; Maguire *et al.*, 1998, 1999). Therefore, evidence of developmental changes both in these brain regions and in relevant memory retrieval processes provides a strong rationale for using navigation paradigms to generate insights on possible relationships between psychological and neural development.

Functional magnetic resonance imaging (fMRI) may prove particularly useful in examining relationships between psychological and neural development. Few fMRI studies consider issues in cognitive development (e.g., Casey *et al.*, 1995; Nelson *et al.*, 2000; Thomas *et al.*, 1999), and none consider developmental aspects of declarative memory retrieval or navigation. Structural

MRI studies document the immature state of temporal and frontal association cortices, brain regions implicated in navigation, and memory retrieval (Giedd *et al.*, 1999; Thompson *et al.*, 2000). While the precise timing of specific developmental changes in these brain areas remains unclear, changes occur over a broad window, extending through adolescence (Jernigan *et al.*, 1991; Pfefferbaum *et al.*, 1994; Sowell *et al.* 1999). The goal of the current study was to use a navigation paradigm to map brain regions engaged during memory retrieval in adolescents and adults.

To accomplish this goal, adolescents, and adults were trained in a virtual reality city. Using fMRI, brain regions engaged during navigation were delineated, while subjects alternately used either memory for city locations (NAV) or arrows appearing in the city (ARROW) to guide their route of travel. Memory-guided navigation is hypothesized to engage brain regions previously implicated in episodic memory retrieval, including medial temporal and prefrontal regions. Moreover, based on prior studies (Maguire *et al.* 1998, 1999, 2000; Spiers *et al.*, 2001), proficiency in navigation across subjects specifically is hypothesized to predict degree of engagement in the right anterior/medial temporal lobe for the NAV/ARROW contrast.

Based on prior studies (Denckla *et al.*, 1980; Silverman and Eals, 1992), adolescents were hypothesized to exhibit immature allocentric memory representations of the virtual reality city, despite having mature navigation ability. We hypothesized that this would be reflected in slower labeling of a previously unseen map depicting the virtual reality city in which subjects had navigated. We used fMRI to examine neural aspects of memory-guided navigation. Based on prior data linking changes within frontal and temporoparietal association cortex to cognitive changes during adolescence (Denckla *et al.*, 1980; Mesulam, 2000), we hypothesized that either developmental status (adolescent vs adult age) or performance on the allocentric memory test would predict degree of engagement within frontal and temporoparietal association cortex for the NAV/ARROW contrast. We hypothesized that *either* developmental status *or* allocentric memory would predict engagement since these two measures were expected to correlate.

METHODS

Subjects

This study recruited 20 right-handed medically and psychiatrically healthy volunteers (10 adolescents, 10 adults). All subjects provided consent/assent, and a parental guardian of all adolescents provided consent. Adolescents were 13.9 ± 1.4 (range 12–16) years old; adults were 28.5 ± 4.3 (range 25–38) years old. Both samples included 5 males.

Navigation Paradigm

The study adapted the virtual reality paradigm used by Maguire *et al.* (1998) and designed by N. Burgess. The identical software depicting the navigation environment was used in the current study as in Maguire *et al.* (1998), but training and task procedures during scanning were simplified to ensure that adolescents could achieve acceptable levels of performance. Prior to scanning, subjects underwent two training sessions. The first session occurred 1 to 2 weeks prior to the fMRI study. This session began with an investigator-led tour through the virtual reality environment, followed by 20 min of free navigation, after which subjects were tested on their ability to navigate. To facilitate memory consolidation, this test was followed by a second tour and a 20-min free navigation period. To meet criteria for study participation, all subjects had to successfully locate three scenes during each of two 2-min navigation periods. The second training session occurred on a separate day, during the same week as the fMRI study. Subjects were allowed 20 min of free navigation and were retested on their navigation ability.

The fMRI experiment consisted of two 5-min runs, each including one 1-min epoch and two 2-min epochs adapted from Maguire *et al.* (1998). As noted above, the experiment used the same virtual reality city software platform as in Maguire *et al.* (1998). In this platform, subjects navigate through an LCD presentation of the virtual reality city as though they are directly walking through the city. In the current study, subjects navigated using an MR-compatible touch pad that interfaced with the software platform.

In the 1-minute epoch (FIX), subjects passively viewed scenes from the virtual reality city. In one 2-minute epoch (ARROWS), subjects navigated through the city by following arrows appearing on the floor of the city to guide their route. In the other 2-minute epoch, subjects used their memory of the virtual city to navigate. This memory for the virtual city layout had been developed during the two previous training sessions that had occurred on separate days from the scanning session. One of these had occurred 1 to 2 weeks prior to scanning, while the second had occurred on the same week of the scanning session.

During the imaging experiment, goal locations appeared during memory-guided navigation on a series of screens hanging on the walls of the city. In the memory-guided epoch, individual screens were illuminated as subjects approached a screen, revealing a picture of another goal location within the town to which subjects were required to navigate. In the current study, but not in Maguire *et al.* (1998), screens showing goal locations remained opaque during the arrow-following task, since there was concern that presenting goal locations during arrow following might confuse adolescent subjects. During the imaging experiment, a trained operator used a parallel video presentation to view the

subject's trajectory through the virtual city. This allowed the operator to rate the subject's performance during memory-guided navigation and record the goal locations successfully reached in the city and the times at which they were reached.

Cognitive processes were assessed both during and after scanning. During scanning, navigation ability was evaluated as the number of goal locations successfully reached in 4 min of memory-guided navigation. Of note, this rating encompasses a collection of processes, including navigation ability as well as dexterity and speed of travel. Twenty minutes after scanning, memory for town locations was tested by showing subjects a previously unseen map of the virtual reality environment containing a series of 15 letters in 15 goal locations. This map presented a novel, two-dimensional aerial-view display of the city. To successfully label this map, subjects had to transpose their knowledge of the virtual reality city, acquired through direct navigation during training and fMRI runs, to this abstracted "allocentric" map of the virtual reality environment. Adults are hypothesized to display greater efficiency in transposing knowledge acquired during direct navigation to the abstracted allocentric map. This greater efficiency is hypothesized to be observable as a greater number of goal locations correctly labeled within a fixed time. Therefore, subjects were given a timed retrieval test, where they were asked to label as many of the goal locations as possible in 60 s. The term "allocentric memory" is used to describe performance on this postscanning test.

fMRI Procedures

All subjects were scanned in a 1.5-T Siemens MRI scanning device. Head movement was restricted by the use of foam padding. The scanning session began with a sagittal localizer followed by a series of test blood oxygen level-dependent (BOLD) scans and manual shim routines. Functional scans were then acquired during navigation using 23 contiguous 5-mm interleaved axial slices, positioned parallel to the AC-PC line and covering the entire brain [64×64 matrix; echoplanar single shot gradient echo T2* weighting (TR = 3000 ms; TE = 40 ms; FOV = 200 mm; $3.125 \times 3.125 \times 5$ -mm voxels)].

Data Analysis

fMRI data preprocessing and statistical analysis used SPM99b (Wellcome Department of Cognitive Neurology) and other routines written in Matlab 5.3.

Motion correction and spatial normalization. Data sets were aligned and visually inspected for evidence of motion or artifacts due to ghosting. Data were discarded for any subject who exhibited motion of 0.8 mm in any direction (one-fourth of a voxel). This resulted in the removal of data sets for two adolescent females, one adult male, and one adult female, leaving eight data

TABLE 1

Relationship of Navigation Ability to Activation in NAV/ARROW Contrast

t_{12} value	Spatial coordinates, x, y, z (mm)	Anatomical region
8.2	0, -86, -32	Cerebellum Medial temporal lobe
7.9	22, -4, -12	Frontal lobe
7.7	-52, 38, 2	Cerebellum
6.4	-48, -62, -34	Cerebellum
6.3	-8, -68, -14	Thalamus
6.1	8, -6, 4	Posterior cingulate/ area 31
6.1	-4, -42, 42	Frontal cortex
6.1	-32, 48, 34	Cerebellum
6.0	-18, -64, -26	Frontal cortex
5.9	24, 0, 24	Frontal cortex
5.6	22, 12, 28	Cerebellum
5.7	-4, -42, 0	Cerebellum
5.7	-38, -4, -44	Putamen
5.6	22, -2, 8	Frontal lobe
5.6	36, 1, 52	Medial temporal cortex
5.6	26, -48, 6	Basal ganglia
5.6	22, 10, 14	Cerebellum
5.6	-40, -64, -14	Midfrontal gyrus
5.4	-54, 28, 24	Medial frontal lobe/ area 8
5.4	-10, 32, 40	Lateral frontal lobe
5.4	-52, 28, 14	Cerebellum
5.4	-20, -70, -14	Frontal lobe/area 47
5.3	-50, 24, 2	Cerebellum
5.3	-38, -48, -32	Thalamus
5.3	-18, 14, 18	Medial frontal lobe
5.3	14, 2, 48	Medial frontal lobe
5.2	-10, 18, 44	Medial frontal lobe

Note. Critical threshold: $t_{12} = 5.2$ (for $\alpha = 0.05$, corrected for multiple comparisons). Smoothness FWHM = $17.2 \times 16.2 \times 17.5$ mm³. Voxel size $2.0 \times 2.0 \times 2.0$ mm³. Spatial coordinates derive from MNI template generated from SPM99 Output.

sets in adolescents and eight data sets in adults. fMRI images were aligned to the mean volume for each subject and were spatially normalized to an echoplanar image template in the same stereotaxic space as the Montreal Neurological Institute template.

Within-subject time series modeling. Subjects were exposed to three conditions during acquisition of fMRI data: FIX, ARROWS, and NAV. Hypotheses concerning fMRI responses in the two age groups were assessed using a simple implementation of random effects tests (Friston *et al.*, 2000; Holmes and Friston, 1998). This involved modeling the different epochs of the fMRI time series with a discrete cosine basis set (order = 3) convolved with the canonical hemodynamic response function provided within SPM99. The coefficients of these waveforms were estimated with ordinary least squares in each voxel of each subject (low-pass filter was hemodynamic response and high-pass filter cutoff was 0.00595 Hz) (Worsley and Friston,

1995). Contrasts images were then created for each subject. These images represented pairwise comparisons of the mean functional responses associated with each of the three conditions. These contrast images were divided by an image representing the subject-specific, voxel time series means, converting the raw data to percentage-change measures (Aguirre and Zarahn, 1998). After this normalization, these contrast images were spatially smoothed with an isotropic gaussian kernel (FWHM = 6 mm).

Between-group (random effects) statistical analysis. The group analysis used the smoothed contrast images as the dependent variable (Friston *et al.*, 1999; Holmes and Friston, 1998). This analysis was restricted to the contrast between NAV - ARROW for two reasons. First, this is the key contrast in Maguire *et al.* (1998) documenting engagement of the medial temporal lobe. Second, the NAV and ARROW conditions require similar levels of motor coordination and visuospatial ability, differing mainly with respect to the cues employed by the subject to guide navigation. In the NAV condition, route of travel is guided by the subject's memory for the city, while in the ARROW condition, route of travel is guided by visual cues appearing directly within the environment. Thus, the two conditions differ mainly in terms of the use of memory to guide navigation.

The smoothed contrast images of all subjects were fit to a second-level model that included three factors: age (adolescent vs adult), number of town sites located during scanning, and allocentric memory for town locations probed after scanning. As the data in this group analysis were actually the effects of tasks on BOLD signal, the age factor in this analysis is identical to an age-by-task interaction in a repeated-measures ANOVA context, predicting task-associated changes in the BOLD signal.

As predicted, age and allocentric memory did in fact exhibit a strong correlation (see Results). Changes in allocentric memory were hypothesized to capture salient aspects of cognitive developmental changes that occur between adolescence and adulthood. Because allocentric memory and age share variance relevant to our neurodevelopmental hypotheses, the most appropriate analysis simultaneously modeled activations as a function of both age and allocentric memory performance. This model presents association between brain activation and age, allocentric memory performance, as well as their combination. Initial hypothesis tests accordingly relied on the F test for the association between activation and both independent measures. Separate t tests then considered the unique associations of activations with either age or memory, controlling for the other variable. While these t tests model more specific associations between activation and either age or memory performance than with the F test, they are less sensitive to associations between activa-

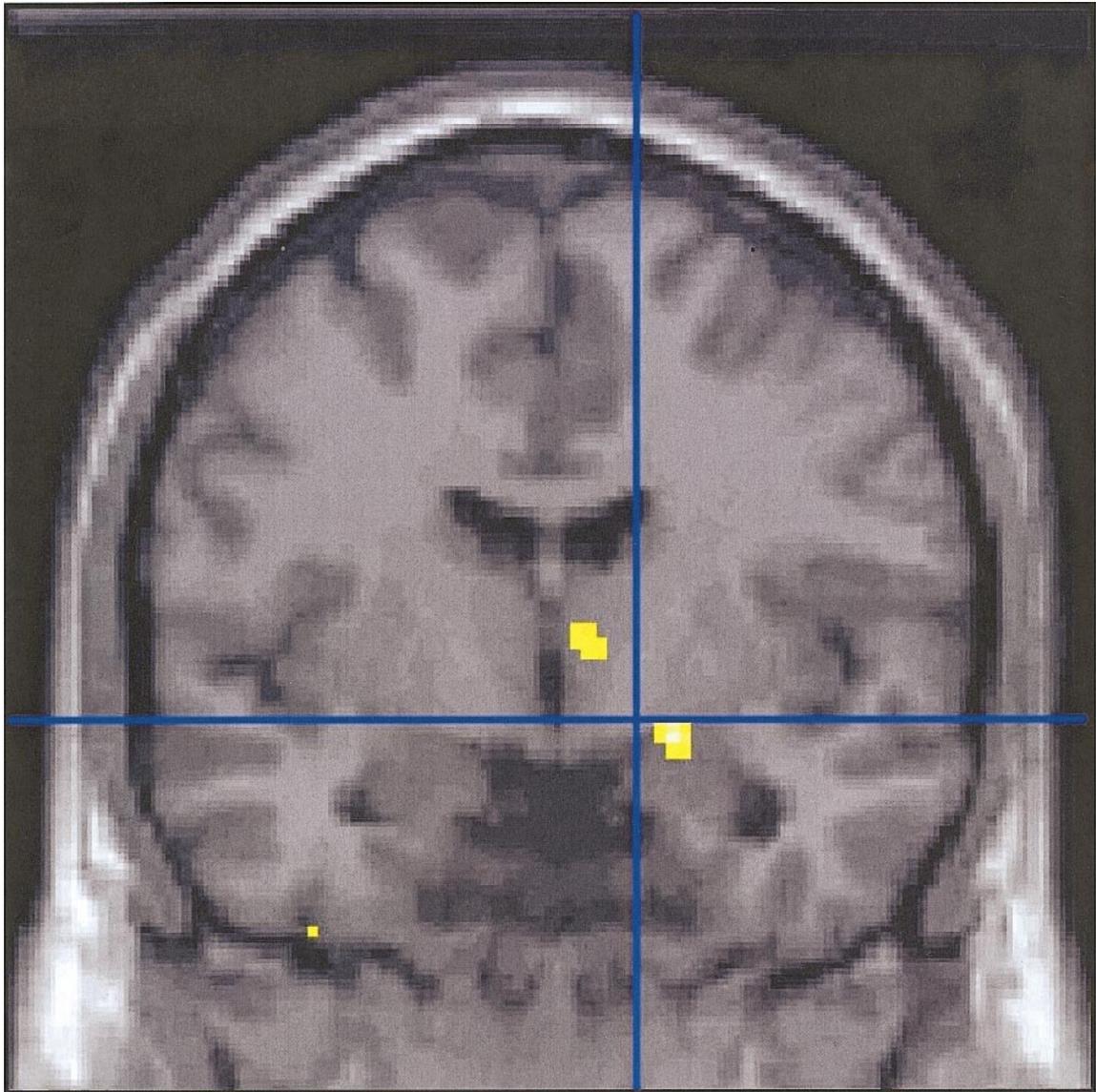


FIG. 1. Navigation ability and medial temporal lobe activation in NAV/ARROW: Coronal slice displaying association across subjects ($n = 16$) between navigation ability and activation in NAV/ARROW contrast. Slice uses Montreal Neurological Institute (MNI) template from SPM99 at the level of the mamillary bodies. Activation is visible on the right side in the thalamus and at the junction of the amygdala and anterior hippocampus (critical $t_{12} = 5.2$; $\alpha = 0.05$, corrected for multiple comparisons). Association is generated in a statistical model including navigation ability, age, and allocentric memory performance as predictors of activation for the NAV/ARROW contrast.

tion and factors that are common to age and memory performance.

We controlled false-positive rates at two-tailed $\alpha = 0.05$ per map (i.e., 0.05 corrected for the multiple spatial comparisons in each map). In theory, one could use the t field thresholds provided by SPM99 to do so (Worsley, 1994). Unfortunately, for typical degrees of freedom and FWHM/(voxel size) ratios, theoretical t field threshold results are far too conservative, leading to increased Type II error rates. Therefore, an approximation to the appropriate t threshold was instead obtained by Bonferroni correction for the number of resolution elements per statistical map, as calculated by SPM99. There were 800 resels per statistical map.

As a result, this led to a t threshold of 5.2 and an F threshold of 18.5, using a P value of 0.05 for each map.

RESULTS

Navigation Ability and Allocentric Memory

While navigating during fMRI scanning in the virtual reality environment, adolescents found on average 9.3 ± 2.7 city locations, while adults found 8.7 ± 3.0 ($t_{14} = 0.5$; $P > 0.20$). In both groups, average performance during scanning exceeded the criterion set during training of finding six locations. After scanning, subjects were asked to label city locations in the allo-

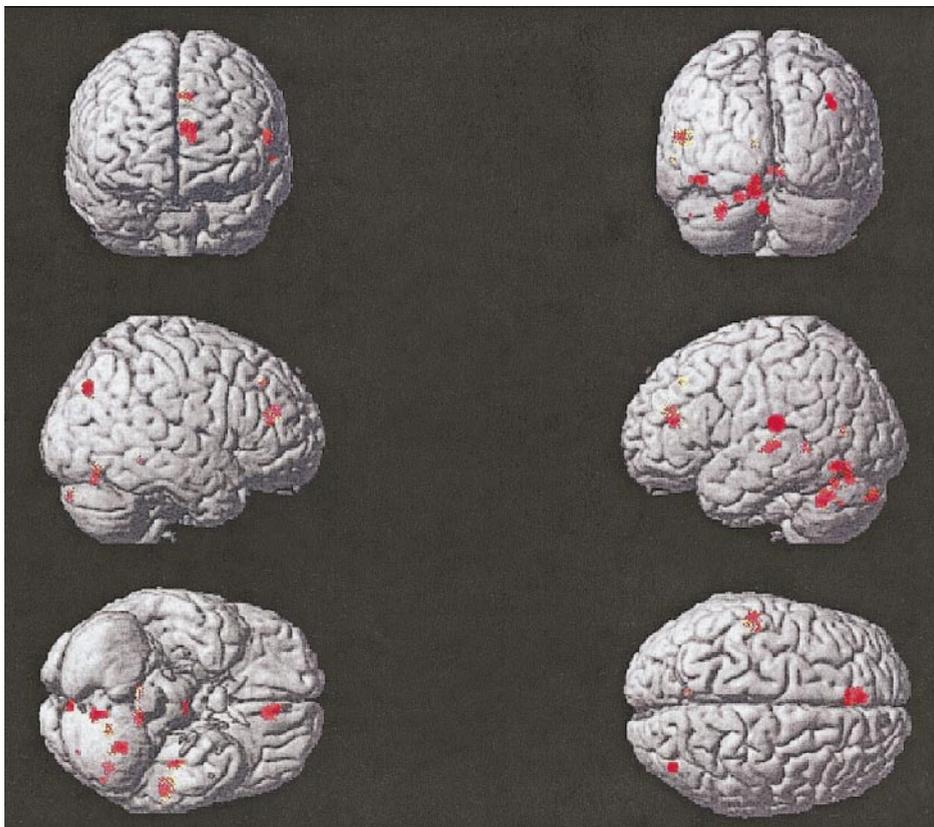


FIG. 3. Development and activation in NAV/ARROW. Developmental associations with brain activation, assessed with an F test for association of age and/or allocentric memory performance with activation in NAV/ARROW contrast (critical $F_{2,12} = 18.5$; $\alpha = 0.05$, corrected). Display uses three-dimensional brain from the MNI template. Results are generated in a statistical model including navigation ability, age, and allocentric memory performance as predictors of activation for the NAV/ARROW contrast.

centric memory test. On this test, adults labeled twice as many locations (9.9 ± 3.8) as adolescents (5.0 ± 2.3) ($t_{14} = 3.0$; $P < 0.01$). Therefore, as predictor variables for functional activation, age and allocentric memory were highly intercorrelated.

fMRI Results

As noted above, fMRI results focus on the contrast of memory vs arrow-guided navigation (NAV/ARROWS). Activation for this contrast was modeled as a function of navigation ability, age group (adolescent vs adult), and performance on the allocentric memory test. A model was also fit including gender, but no associations emerged between brain activation patterns and gender.

Navigation ability. Table 1 presents Talairach coordinates for maxima generated from a statistical parametric map for the correlations between memory-guided navigation ability, quantified as the number of locations found during scanning, and degree of activation in the NAV/ARROW contrast ($P < 0.05$, corrected for multiple comparisons). These results are adjusted for the effects of age and allocentric memory performance, which are included in the statistical model. As shown in Table 1, memory-guided navigation ability

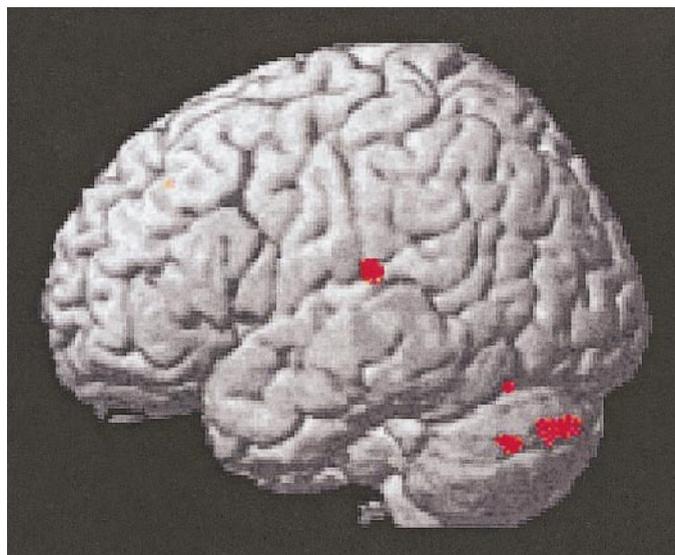


FIG. 4. Age and activation in NAV/ARROW: Association between age and activation in NAV/ARROW contrast (critical $t_{12} = 5.2$; $\alpha = 0.05$, corrected). Display uses three-dimensional brain from the MNI template. Results are generated in a statistical model including navigation ability, age, and allocentric memory performance as predictors of activation.

related to activations in various brain regions. The two strongest maxima lay within the medial temporal lobe and the cerebellum. Specifically, a correlation emerged in the right medial temporal area, at the amygdala-hippocampal junction (spatial coordinates: $x = 22$, $y = -4$, $z = -12$), such that subjects finding more town locations exhibited higher activation (see Figs. 1 and 2). A series of strong correlations also arose in the cerebellum. Other correlations emerged within the frontal lobe, encompassing Brodmann areas 8 ($x = -10$, $y = 32$, $z = 40$) and 47 ($x = -50$, $y = 24$, $z = 2$), the posterior cingulate gyrus [area 31 ($x = -4$, $y = -42$, $z = 42$)], the basal ganglia, and thalamus (see Fig. 1 for thalamus activation). In all of these regions, better performance predicted stronger activation.

Development and activation. Initial statistical tests for developmental effects relied on an F test for the two intercorrelated variables of age and allocentric memory performance, objectified as the number of sites labeled on an aerial display after scanning. This initial analysis was performed to display areas of activation associated with age, allocentric memory performance, or their combination. This analysis also included memory-guided navigation ability to control for associations between navigation ability and activation while modeling the association between development and activation. As noted above, relative to this analysis based on an F test, analyses examining associations with only age or allocentric memory with t tests would be less sensitive to activations associated with factors common to age and allocentric memory performance. Figure 3 and Table 2 present results from an analysis which tests for a correlation of age and/or allocentric memory with NAV/ARROWS activation.

Figure 3 shows that the NAV/ARROW contrast differentially engaged the left hemisphere as a function of either age or allocentric memory performance. Correlations emerged with activation in the temporoparietal junction ($x = -52$, $y = -26$, $z = 14$), the cerebellum, and a region encompassing the posterior cingulate, parahippocampus, and posterior hippocampus ($x = -6$, $y = -42$, $z = 0$). Correlations also emerged with activation in anterior cingulate [area 32 ($x = -8$, $y = 38$, $z = 14$)], the brain stem, and association cortex of the frontal [area 8 ($x = -4$, $y = 34$, $z = 40$); area 9 ($x = -4$, $y = 42$, $z = 22$)], medial/posterior temporal [area 37 ($x = -40$, $y = -20$, $z = -2$); area 22 ($x = -60$, $y = -26$, $z = 0$)], and parietal lobes [area 19 ($x = 40$, $y = -76$, $z = -36$)].

An effort was made to decompose associations detected with the F test by using t tests. Each of the two t tests examined associations that either age group or allocentric memory performance exhibited with brain activation patterns, independent of navigation ability, as well as allocentric memory (for the analysis with age group as the predictor) or age group (for the analysis with allocentric memory as the predictor). In the anal-

ysis controlling for navigation ability and allocentric memory performance, Fig. 4 and Table 3 present brain regions where adolescents differed from adults, with adolescents consistently showing greater activation than adults. Maxima lay in the temporoparietal junction ($x = -54$, $y = -26$, $z = 14$), frontal cortex ($x = -2$, $y = 34$, $z = 40$), posterior parietal cortex ($x = 40$, $y = -76$, $z = 38$), cerebellum, brain stem, and thalamus. Controlling for age and navigation ability, two correlations in the cerebellum emerged with allocentric memory [($x = -2$, $y = -86$, $z = -32$; $t = 6.50$); ($x = -8$, $y = -68$, $z = -12$; $t = 5.21$)]. With both correlations, better performance on the memory test correlated with reduced levels of activation.

DISCUSSION

Three findings emerged from this study. First, adolescents and adults exhibited comparable ability to find goal locations when directly navigating from memory in the virtual reality environment, but adults exhibited superior ability to transpose their knowledge of the virtual reality environment to allocentric space. Second, memory-guided navigation ability during scanning positively correlated with activity in various brain regions, including a right medial temporal region. Finally, adolescent age predicted the degree of activation in temporoparietal and frontal cortex, as well as the cerebellum.

With respect to behavioral data, the current age-related differences in ability to label a map of the virtual reality city are consistent with previous data on developmental aspects of map-guided, as opposed to real-world, navigation (Cohen and Scheupfer, 1980; Denckla *et al.*, 1980; Overman *et al.*, 1996; Silverman and Eals, 1992). The ability to maneuver directly within a novel environment matures earlier than the ability to navigate using a two-dimensional map of the environment (Mathews, 1992). Moreover, map-guided navigation represents a specific example of a broader set of skills requiring extrapolation between abstract representations and actual constructs. The ability to perform such extrapolations begins to reach maturity in adolescence, allowing adolescents to deploy increasingly complex descriptive systems and classification schemes in the service of various forms of abstract thought (Goldberg and Costa, 1981; Fuster, 1997; Keating, 1990; Keating and Sasse, 1996). The availability of efficient classification schemes in adults is thought to enable extrapolation over a broad set of contextual cues (Goldberg and Costa, 1981). These developmental changes might be manifest as more rapid labeling of an allocentric map and developmentally distinct patterns of brain activation in the current study.

Language represents a particularly efficient means for deploying descriptive systems, and adolescent maturation in linguistic skill reflects developmental

changes in descriptive systems. Therefore, the superior performance of adults on the allocentric memory test is hypothesized to parallel their superior verbal abilities. Goldberg and Costa (1981) suggested that deployment of descriptive systems favoring the left hemisphere relates to a range of skills extending beyond language per se, with prominent examples including knowledge of musical notation and the rules of chess. Spatial map construction may offer a similar example. This does not necessarily rule out the possibility that superior verbal abilities may also affect the strategies used by adults in the current navigation experiment. Future studies might attempt to directly probe differences between adolescents and adults in the application of explicit verbal compared to nonverbal strategies that may be used during virtual reality navigation.

With respect to data on neural correlates of memory-guided navigation skill, the current findings are also consistent with previous findings. While at least four other groups have mapped regions engaged during memory-guided navigation (Aguirre *et al.*, 1996; Aguirre and D'Esposito, 1997; Gron *et al.*, 2000; Hsu *et al.*, 2000), Maguire *et al.* (1998) provide the most relevant data. The current study adapted PET-based methods from Maguire *et al.* (1998) to the fMRI environment, facilitating research on development due to the safety of fMRI. Training procedures were altered and the arrow-following task was simplified so that procedures could be mastered by both 13-year-olds and adults. The current study also relied on a more general index of navigation than in Maguire *et al.* (1998). In the current study, navigation ability correlated across subjects with activity in a right medial temporal region ($x = 22$, $y = -4$, $z = -12$). In Maguire *et al.* (1998), Talairach coordinates of the nearest relevant maximum lay at $x = 36$, $y = -12$, $z = -20$. Given differences across the studies, similarities in results support the reliable nature of an association between navigation performance and right anterior/medial temporal engagement across subjects.

In the current study, navigation ability also related to activations in the cerebellum, frontal cortex, cingulate gyrus, caudate, and thalamus. Prior studies among rodents and humans implicate the cerebellum in mnemonic processes, including memory-guided navigation (Gron *et al.*, 2000; Hsu *et al.*, 2000; Middleton and Strick, 1994; Molinari *et al.*, 1997). Previous imaging studies also implicate various relevant cortical and subcortical brain regions in attentional and mnemonic processes engaged during memory-guided navigation (Cabeza and Nyberg, 2000; Desmond *et al.*, 1997; Fletcher *et al.*, 1997; Lepage *et al.*, 1998; Maguire *et al.*, 1998). While these prior studies find that a range of brain regions may be engaged during navigation, distinct regions may be engaged by specific component process. For example, speed of travel through the environment may relate most closely to caudate engagement (Maguire *et al.*, 1998), whereas rate of change in

the visual domain may relate to medial temporal engagement (Hsu *et al.*, 2000).

With respect to data on neurodevelopmental aspects of mnemonic processes, only a handful of previous fMRI studies examine any issues pertinent to cognitive development (Casey *et al.*, 1995; Nelson *et al.*, 2000; Thomas *et al.*, 1999). These prior studies typically document engagement of similar brain regions in children and adults during attention tasks. As in these prior studies, the current study demonstrates the viability of fMRI studies of relationships between brain activity and cognitive processes in pediatric populations. The current study also possesses a few relatively novel features. Specifically, the report delineates differences between adolescents and adults in the degree to which brain regions are engaged during memory-guided navigation, a process that interrelates aspects of episodic memory retrieval (Maguire *et al.*, 1998, 1999, 2000), brain plasticity (Cohen and Eichenbaum, 1994; Gould *et al.*, 1999a,b), and adolescent cognitive development (Denckla *et al.*, 1980; Fuster, 1997; Keating, 1990).

In the current study, adolescent age specifically predicted enhanced activation in left temporoparietal cortex. This finding is consistent with historical emphasis on the role of left-sided temporoparietal maturation in adolescent cognitive development (Geschwind and Galaburda, 1985). Consistent evidence of adolescent development in temporal and parietal cortical association areas emerges both from nonhuman primate studies and human structural MRI studies (Goldberg and Costa, 1981; McGlashan and Hoffman, 2000; Mesulam, 2000). As noted above, adolescent cognitive development involves changes in the use of abstract representations to facilitate performance on specific cognitive tasks, such as memory retrieval. Consistent with fMRI data in the current study, prior theories specifically emphasize the role of temporoparietal maturation in supporting such cognitive changes (Geschwind and Galaburda, 1985; Goldberg and Costa, 1984).

Age also related to activation in the dorsal prefrontal area, consistent with emphasis on the role for prefrontal maturation in adolescent cognitive changes (Casey *et al.*, 1995, 2000; Nelson *et al.*, 2000; Thomas *et al.*, 1999). Finally, both age and allocentric memory performance also specifically related to cerebellar activation. This finding is consistent with recent emphasis on the role for cerebrotocerebellar circuitry in developmentally linking areas of association cortex (Levisohn *et al.*, 2000; Middleton and Strick, 1994).

Given the scarcity of developmental studies, more fMRI research is needed on factors that could potentially contribute to apparent age-related differences in cortical association and cerebellar engagement detected in the current study. Such findings could arise from various factors, including differences in hemodynamics, brain structure, task demands, or changing relationships among brain regions engaged by one or another task. For example, changes in synaptic density

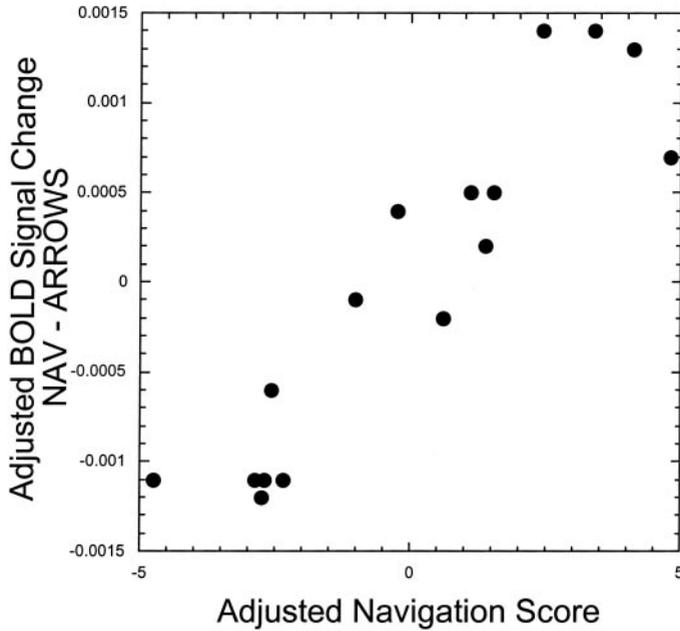


FIG. 2. Cross-subject association between navigation score and medial temporal activation. Scatter plot for association between navigation ability and right-sided medial temporal lobe activation in NAV/ARROW contrast displayed in Fig. 1 ($n = 16$). Both variables are adjusted for age and allocentric memory, which serve as predictor variables in the model, along with navigation score. Spatial coordinates for region are $x = 22$, $y = -4$, $z = -12$, corresponding to right anterior medial temporal lobe at the junction of the amygdala and anterior hippocampus.

and myelination occur well into adolescence (McGlashan and Hoffman, 2000; Mesulam, 2000). Such changes could potentially alter activation patterns in fMRI experiments. In some instances, this might produce stronger activations in adolescents, through greater synaptic density that provides more substrate for changes in the BOLD signal. In other instances, this might produce stronger activations in adults, where more focal engagement of a brain region might occur through refinements in synaptic connectivity.

Because recent studies have begun to delineate specific developmental changes in various mnemonic processes (Cycowicz *et al.*, 2000; Nelson *et al.*, 2000), more fMRI research is specifically needed on associations between mnemonic processes and adolescent brain function. In the current study, as in Maguire *et al.* (1998), poorer performance in memory-guided navigation predicted *reduced* anterior/medial temporal activation. However, both adolescent age and poorer performance on the allocentric memory test predicted *enhanced* activation in other brain regions. As in other fMRI studies (Bookheimer *et al.*, 2000; Casey *et al.*, 2000; Cabeza and Nyberg, 2000; Callicott *et al.*, 1999), these data highlight the complex relations of brain activity with behavioral performance. Some investigators suggest that less competent performance in mne-

monic tasks can be associated with greater recruitment of relevant neural systems (Bookheimer *et al.*, 2000; Callicott *et al.*, 1999). Interestingly, Bookheimer *et al.* (2000) postulate a specific association in this respect between heightened activation within left-lateralized brain systems and inefficient memory retrieval processes. If this interpretation is valid, adolescents in the current memory retrieval study may be seen as exhibiting increased recruitment of immature left-hemisphere task-relevant systems, while adults may already have developed more efficient mechanisms for the extraction of invariant allocentric spatial maps. As such, findings from the current study may generate interest in continued research on relationships between changes in brain activity and developmentally sensitive cognitive processes.

The current study has at least four limitations that could be addressed in subsequent research. First, the study possessed a small overall sample size, as well as small subsamples of males and females. While small sample sizes are typical in developmental fMRI studies (Casey *et al.*, 1995; Nelson *et al.*, 2000; Thomas *et al.*, 1999), such small samples limit statistical power to detect both task-associated changes in BOLD signal as well as between-group differences in BOLD signal change. As a result, negative findings in the current study, such as the absence of gender-specific changes in BOLD signal, should be interpreted cautiously. Second, the current study relied upon standard procedures for voxelwise analyses, involving spatial normalization

TABLE 2

Relationship of Age and Allocentric Memory with NAV/ARROW Contrast

$F_{2,12}$	Spatial coordinates, x, y, z (mm)	Anatomical region
45.0	-6, -42, 0	Hippo-/parahippocampus
35.6	-52, -26, 14	Temporoparietal cortex
35.1	40, -76, 36	Parietal association cortex
35.0	-8, 38, 14	Anterior cingulate
33.2	-4, 42, 22	Frontal cortex/area 9
33.4	-8, -68, -12	Cerebellum
31.1	-8, -72, -22	Cerebellum
28.6	-2, -86, -32	Cerebellum
28.4	-40, -62, -14	Cerebellum
28.4	-18, -62, -24	Cerebellum
28.4	-28, -56, -32	Cerebellum
25.5	-4, -14, -10	Brainstem/midbrain
25.5	8, -44, -8	Cerebellum
23.9	-4, 34, 40	Frontal cortex/area 8
22.1	-8, -68, 10	Occipital cortex
21.8	-40, -20, -2	Temporal cortex
20.1	-32, -82, -34	Cerebellum
19.8	-60, -26, 0	Temporal cortex
19.2	-48, -66, -36	Cerebellum

Note. Critical threshold: $F_{2,12} = 18.5$ (for $\alpha = 0.05$, corrected for multiple comparisons). Smoothness FWHM = $17.2 \times 16.2 \times 17.5$ mm³. Voxel size $2.0 \times 2.0 \times 2.0$ mm³. Spatial coordinates derive from MNI template generated from SPM99 Output.

TABLE 3

Relationship of Age with Activation
in NAV/ARROW Contrast

t_{12}	Spatial coordinates, x, y, z (mm)	Anatomical region
6.9	-4, -14, -10	Brainstem/midbrain
6.3	-54, -26, 14	Temporoparietal cortex
6.2	-48, -66, -36	Cerebellum
6.2	-32, -82, -34	Cerebellum
5.8	40, -76, 38	Parietal cortex
5.7	-24, -84, -32	Cerebellum
5.6	14, -10, -10	Medial temporal cortex
5.3	-2, 34, 40	Frontal cortex/area 8
5.2	-46, -66, -20	Cerebellum

Note. Critical threshold: $t_{12} = 5.2$ (for $\alpha = 0.05$, corrected for multiple comparisons). Smoothness FWHM = $17.2 \times 16.2 \times 17.5$ mm³. Voxel size $2.0 \times 2.0 \times 2.0$ mm³. Spatial coordinates derive from MNI template generated from SPM99 Output.

in adolescents as well as adults. Due to changes in brain morphology, these procedures may differentially affect data in adolescents and adults. Nevertheless, the magnitude of morphometric differences between adolescents and adults are considerably smaller than the differences in BOLD signal change documented in the current study. Third, the current study used a cross-sectional approach to examine developmental issues. In general, cross-sectional designs provide potentially important initial insights on relevant developmental processes. However, longitudinal research designs enable a more compelling analysis of such processes (Kraemer, 2000). Given the current developmental findings, future longitudinal studies might examine changes in the lateralization of activation patterns during repeated episodes of spatial navigation or other forms of memory retrieval. Such future might also grapple with the role of age as opposed to puberty in such developmental changes in activation. Given the strong relationship between age and puberty, future studies will either require large sample sizes or unique designs that select age-matched subjects discordant on puberty. Finally, in the current study, subjects navigated within an elaborate, dynamic stimulus array depicting the virtual reality city. Such an elaborate presentation might facilitate efforts to simulate real-world navigation in an fMRI environment while also facilitating efforts to engage adolescent subjects in the experiment (Maguire *et al.*, 1999). Nevertheless, the use of such elaborate stimuli engender inherent confounds in experiments, given the effects of complex stimuli on the engagement of brain regions involved in perception. As a result, future efforts to replicate and extend these results might attempt to use simpler, less elaborate stimuli to probe aspects of navigation or spatial abilities across developmental groups.

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