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Learning of serial digits leads to frontal activation in functional MR imaging

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PURPOSE
Clinical studies have shown that performance on the serial digit learning test (SDLT) is dependent upon the mesial temporal lobes, which are responsible for learning and its consolidation. However, an effective SDLT performance is also dependent upon sequencing, temporal ordering, and the utilization of mnemonic strategies. All of these processes are among the functions of the frontal lobes; in spite of this, the relationship between SDLT performance and the frontal lobes has not been demonstrated with previously used mapping techniques. The aim of this study was to investigate the areas of the brain that are activated by SDLT performance.

MATERIALS AND METHODS
Ten healthy, right handed volunteers (mean age, 20.1 years; SD: 3.3) who had 12 years of education were studied with a 1.0 T MR imaging scanner. BOLD (blood oxygen level dependent) contrast and a modified SDLT were used. Activated loci were automatically mapped using a proportional grid.

RESULTS
In learning, the most consistent activation was observed in B-a-7 of the right (80%) and the left hemispheres (50%). In recall, the most consistent activation was observed in B-a-7 of the right hemisphere (60%). Activations were observed in 2.5±0.97 Talairach volumes in learning, whereas they encompassed 1.7±0.95 volumes in recall. The difference between both phases (learning and recall) regarding total activated volume was significant ($p<0.05$).

CONCLUSION
The prefrontal activation during SDLT performance was not related to learning or to recall, but to a function that is common to both of these cognitive processes. A candidate for this common factor may be the executive functions, which also include serial position processing and temporal ordering.

Key words: • *sequencing* • *temporal ordering* • *frontal lobe* • *prefrontal area* • *functional magnetic resonance imaging* • *serial digit learning test*

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Tasks that involve digit series are among the primary tools of neuropsychology for measuring attention, learning, and memory, since the contaminating effect of associative influences is lower on digits than on words or pictures (1, 2). A neuropsychological test that measures the specified functions is the serial digit learning test (SDLT). This test is comprised of a series of orally presented digits that the testee should learn and repeat in their given order (3). The series is comprised of 9 digits; this normally exceeds the memory span of even healthy young adults (4, 5). Accordingly, SDLT performance requires the utilization of mnemonic strategies.

Studies of clinical samples demonstrated that performance on SDLT is dependent upon the mesial temporal lobe and hippocampus (6). This is to be anticipated since these areas are, by scientific consensus, related to memory, specifically to consolidation of recently learned material (2, 7). However, SDLT performance requires a number of processes that are closely related to the frontal lobes. The repetition of SDLT digits in their correct order is an issue of serial position processing (2). This processing is, in turn, related to the ability to sequence and to temporally order events.

Sequencing and temporal ordering are closely related to the functioning of the frontal lobes, and, specifically, the prefrontal region (8, 9). The formulation of temporal organizational structures, which are necessary to learning and memory, was shown to be related specifically to the dorsolateral prefrontal cortex (DLPFC) (10). Accordingly, the serial position effect is altered in patients with DFLPFC lesions (11). The performance of these patients did not show the U-shaped serial learning curve; the primacy and recency effects were abolished and the curve flattened out.

Serial position processing also involves proactive interference (PI); digit span was, in fact, found to be influenced by PI manipulations (12). Susceptibility to interference was, accordingly, found to be related to the orbitofrontal (OFC) region of the prefrontal cortex (11). Another finding that pointed to the role of the frontal lobes in serial processing was the developmental period in which the maximum digit-span score is obtained. This period is adolescence (4), the developmental stage during which the frontal lobes and, specifically, the prefrontal cortex develop (13). Since the digit span is limited (4, 5), humans utilize organizational or mnemonic strategies when confronted with such a task, which are also functions of the frontal lobes (1).

The goal of the present study was to test the hypothesis that serial digit learning is related to frontal lobe activation. The activation areas were determined using functional magnetic resonance imaging (fMRI) and serial digit learning was assessed using motor-SDLT.

Materials and methods

Ten healthy volunteers (7 females, 3 males) who were 18 to 21 years of age (mean, 20.1±3.3) and had 12 years of institutional education served as subjects. Informed consent was obtained in all steps of the study (for both formal neuropsychological assessment and the fMRI) and appropriate institutional approval was obtained. As assessed by the Edinburgh Inventory, they were all right-handed. Data were obtained using a 1.0 T (+/-20 mT/m) MR imaging scanner (Magnetom Impact Expert, Siemens, Erlangen, Germany) and a standard quadrature head coil. The study used blood oxygen level dependent (BOLD) contrast method; this method is based on MR signal intensity changes that result from the changing level of oxygenation in regional blood vessels that follow cortical activation (14, 15).

The study used a modified version of the serial digit learning test. SDLT is comprised of a 9-digit series (SD-9), which the tester presents orally at the rate of 1 digit per second. The testee is reminded that he/she should use an appropriate strategy for learning such a long digit series and, one second after the completion of the series, should report the digits in their correct order. This procedure is terminated when the whole series is correctly repeated in two consecutive trials, or when the testee cannot meet this criterion in 12 consecutive trials. However, oral responses in SDLT lead to head movements that may exceed the limit that fMRI technology can tolerate and, in extreme situations, can be responsible for almost the entire fMRI signal (16). In order to overcome this contamination, a variant of SDLT, motor-SDLT, was developed. In this variant that we used, the test was administered aurally using MR compatible ear-phones and the subjects gave their responses with their dominant hand by tracing each digit on a pad. This virtual expression sufficiently eliminated the artifacts that result from head movement.

Using motor-SDLT, stimulus presentation and motor expression occurred, as with the conventional form, at the same rate per second. Before the experiment, pilot studies were performed in which subjects were given training on an alternate series of the SDLT for completing the whole series in 12 seconds. Audibility of the instructions were also confirmed with pseudo-acquisition trials.

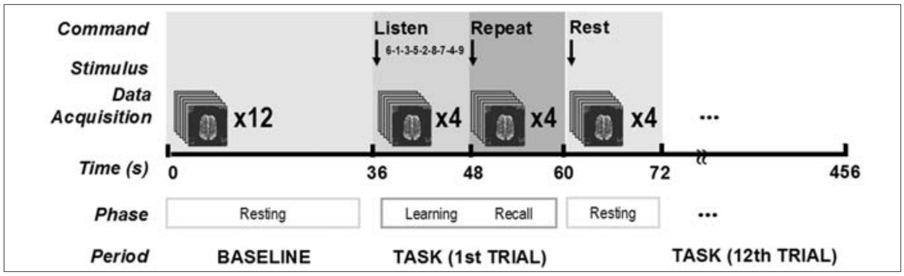

Figure 1. Block diagram of the activation paradigm in the SDLT experiment.

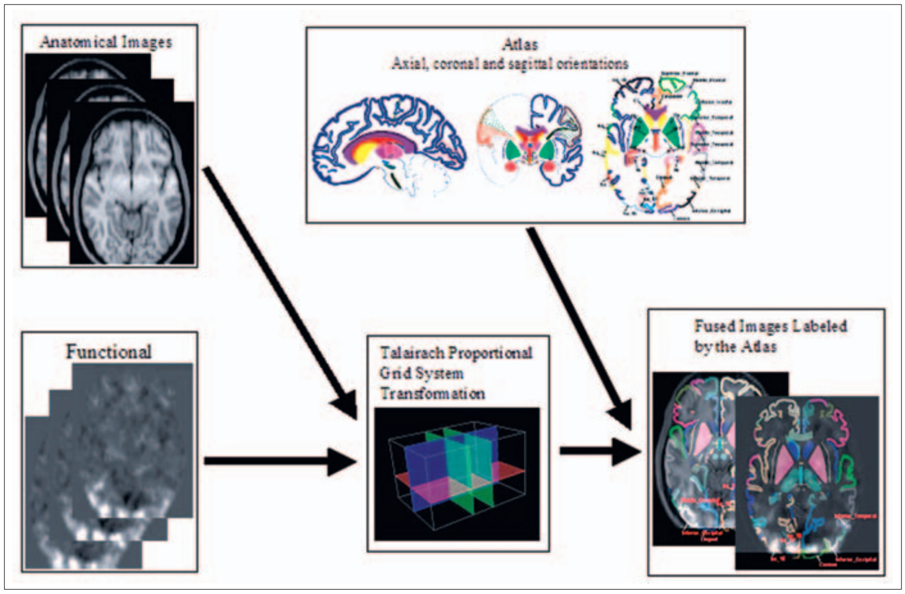

Figure 2. Schematic representation of the steps taken in electronic brain mapping.

Motor-SDLT consisted of two phases: the learning phase in which the 9 digits of the SDLT (SD-9) were administered, and the recall phase in which subjects manually repeated the series. The activation protocol during fMRI was comprised of a baseline-resting period (no activation) of 36 seconds in duration and 12 task periods (activation); each period was 24 seconds in duration. These task periods were comprised of 12 seconds for the learning phase and 12 seconds for the recall phase. The onset and termination of each phase was marked by the instructions "listen" and "repeat", respectively. Additional resting periods 12 seconds in duration were administered after every task period, excluding the last task period (see reference 17 for details of methodology).

The anatomical reference images consisted of 10 contiguous spin echo T1-weighted paraxial sections that were parallel to the bicommissural plane; this covered the frontal lobes from their ventral surface to the vertex with 6 mm slices and 3 mm interslice gaps. With the above-mentioned parameters, every consecutive image represented almost a unique level of the Talairach stereotactic coordinate system (also known as proportional grid system), changing from level 2 to 11 (18). This system is one of the most widely used reference systems, which is keyed to the location of an asset of anatomical landmarks (commissura anterior-commissura posterior, CA-CP) within the cerebrum. In this system, the brain is divided into orthogonal parallelograms, the dimensions of which vary with the principal axes of the brain. Each volume is defined by its three dimensions (indicated by a capital letter, a lower case letter, and a number, e.g., A-a-1 as sector-band-level, respectively).

Functional imaging was performed in identical sections, using free induction decay T2* single-shot gradient-echo echo planar imaging (EPI) MR sequences. Scan-time for each of the 10 contiguous functional sections was

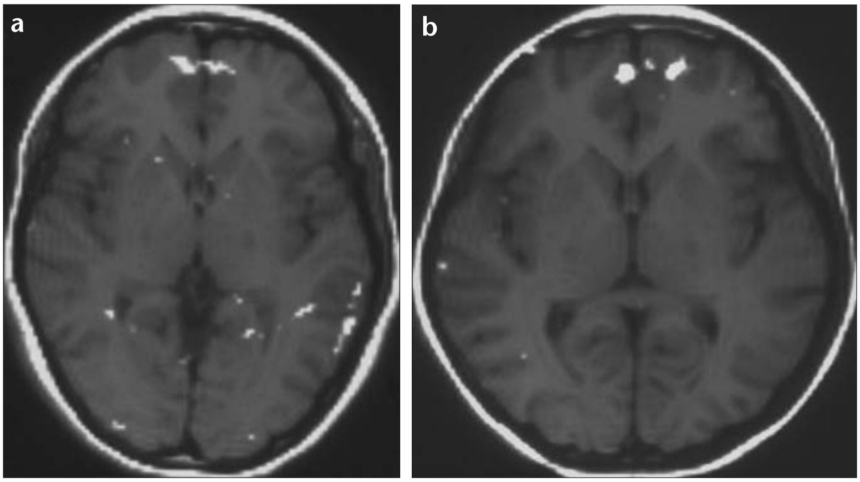

Figure 3. a, b. Functional MR images showing bilateral frontal activations caused by the learning phase of motor-SDLT in two different subjects.

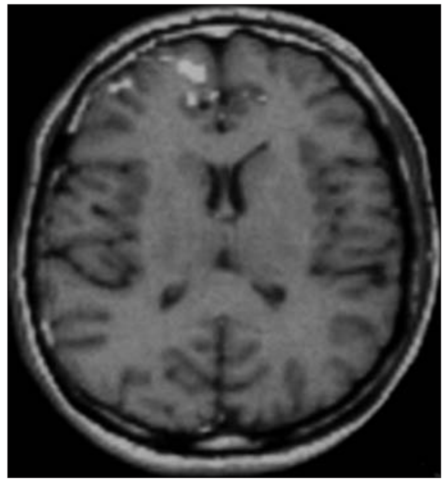

Figure 4. Functional MR image showing unilateral activation caused by the recall phase of motor-SDLT.

Table. Significantly activated areas in the learning and recall phases of SDLT performance.

Phase	Talairach coordinates[a]	Gyri	Broadmann's areas	Occurence (% subjects)
Learning	R-B-a-8	Cingulate	10	30
	R-B-a-7	Cingulate, Superior frontal	9-10	80
	R-B-a-6	Superior frontal, Cingulate	9	20
	R-B-a-5	Superior frontal	9	10
	R-B-a-4	Superior frontal	8	10
	L-B-a-8	Cingulate	10	20
	L-B-a-7	Cingulate, Superior frontal	9-10	50
	L-B-a-6	Superior frontal, Cingulate	9	20
	L-B-a-5	Superior frontal	9	10
Recall	R-B-a-8	Cingulate	10	20
	R-B-a-7	Cingulate, Superior frontal	9-10	60
	R-B-a-6	Superior frontal, Cingulate	9	10
	R-B-a-5	Superior frontal	9	10
	R-B-a-4	Superior frontal	8	10
	L-B-a-8	Cingulate	10	10
	L-B-a-7	Cingulate, Superior frontal	9-10	30
	L-B-a-6	Superior frontal, Cingulate	9	10

[a] R and L refer to the right and left hemispheres, respectively.

2 seconds; this procedure was repeated every 3 seconds. The acquisition parameters for the functional images were TR/TE: 1.8/66 msec; NEX: 1; FOV: 220x220; matrix: 64x64 interpolated to 128x128; slice thickness: 6 mm; interslice gap: 3 mm. With the abovementioned parameters, a total of 152 functional series, each consisting of 10 consecutive slices (total of 1520 images) was acquired during a 456 seconds trial (Figure 1).

The resulting series of images were analyzed with the general linear model, which yielded z-statistics to extract signal changes that correlated with the task performance. In line with the standard administration of motor-SDLT, data including the two consecutively correct trials were analyzed. To control for early signal decrease, data from the first two images of the baseline-resting period were discarded. A second order temporal smoothing was applied to the data to account for event-related latencies and rise times of BOLD response. The threshold (z-score) was set above 3.0 to discard independent pixel fluctuations. Temporally correlated changes in signal intensity in rest-task (learning + recall), rest-learning, and rest-recall sets were displayed as bright pixels and were superimposed onto corresponding anatomical MR images. Using the electronic version of the proportional grid system (Brain Atlas for Functional Imaging, Clinical and Research Applications, Kent Ridge Digital Labs, Singapore), superimposed images were then analyzed for localization and naming of the activated areas (Figure 2).

Results

All subjects were able to reach the criterion of two consecutively correct repetitions. The number of repetitions for reaching the criterion varied between 1 and 11. The respective scores varied between 4 and 24 (16.6±6.2). Rest-learning sets were used for detecting the activated brain regions in the learning phase. fMRI images showed bilateral hippocampal activation. The remaining areas that showed significant activations had the following Talairach coordinates: B-a-4 to 8 in the right hemisphere and B-a-5 to 8 in the left (Figure 3 and Table). The most consistent activation was observed in B-a-7 in the right (80% of the subjects)

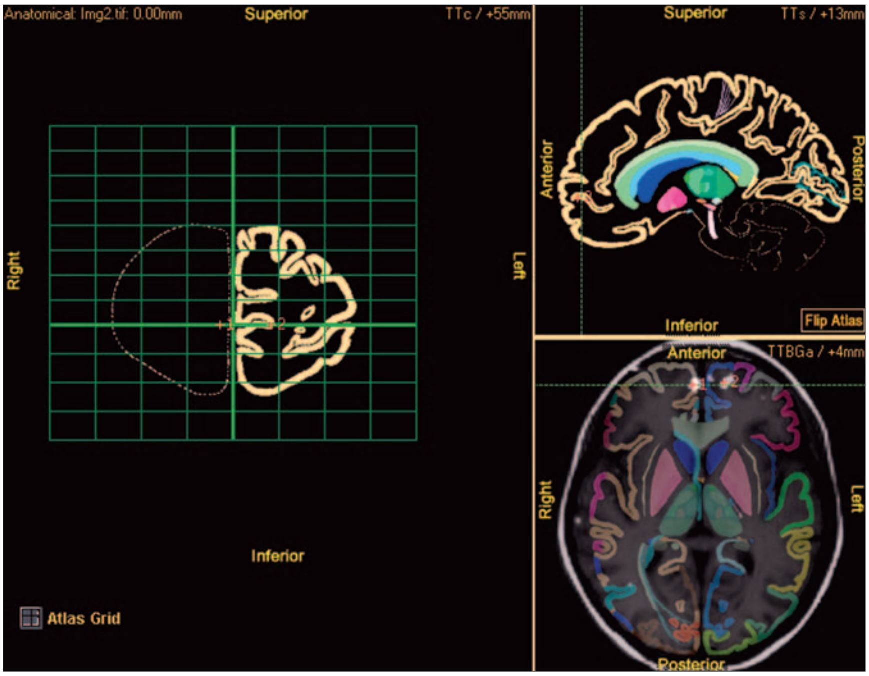

Figure 5. Electronic mapping of the activated loci on coronal *(left),* sagittal *(upper right),* and axial *(lower right)* planes.

Figure 6. General relationship of activated loci and Brodmann's areas on the proportional grid.

and left (50% of the subjects) hemispheres.

Rest-recall sets were used for detecting the activated brain regions in the recall phase. fMRI images showed bilateral hippocampal activation. The remaining areas that showed significant activations had the following coordinates: B-a-4 to 8 in the right hemisphere and B-a-6 to 8 in the left (Figure 4 and Table). The most consistent activation was observed in B-a-7 of the right hemisphere (60% of the subjects). Unlike the learning phase, B-a-7 of the left hemisphere was activated in the recall phase in only 30% of the subjects.

Activations were observed in 1 to 4 (2.5±0.97) Talairach volumes in the learning phase, whereas they encompassed 1 to 4 (1.7±0.95) Talairach volumes in the recall phase. The difference in total activated volume between both phases was statistically significant (paired samples t-test, $p<0.05$). As noted above, activated areas were notably larger during the learning phase of the task. These activations were observed at the medial regions of the frontal lobe, which were mapped to Brodmann's areas 9 and 10 and the superior frontal and cingulate gyri, respectively (Figures 5 and 6, Table).

Discussion

In the present study, we found that serial digit learning involves the activation of not only the hippocampus, but also the prefrontal regions of the brain. Prefrontal activation was such that during both learning and recall, similar regions were covered (Brodmann's areas 8 to 10), areas were similarly organized in the two hemispheres, and, by way of inter-subject consistency, there was a focal area that covered the superior frontal and cingulate gyri (Brodmann's areas 9 and 10). Although more than half of the activations were 10-20% of occurrence, which is quite an unreliable effect in the subject population, bilateral B-a-7 activations in the learning phase and right B-a-7 activation in the recall phase were consistent across subjects. Such findings suggest that the prefrontal activation in the serial digit task was not related to learning or to recall, but to a function that is common to both of these cognitive processes. A candidate for this common factor may be executive functioning; as the term "frontal metaphor" describes, these functions are related to the functioning of the frontal lobes and, specifically, the prefrontal area (19). Serial position processing, temporal ordering, PI interference, and utilization of mnemonic strategies are among the processes that are implicated in serial digit learning/recall (2, 8-11, 13, 16). These processes are, in fact, included under the umbrella of executive functions, which include temporal and spatial organization, sequencing of events, response inhibition and resistance to inhibition, scanning memory, working memory, planning, maintaining and changing sets, usage of mnemonic and organizational strategies, reasoning, and problem solving (19, 20). DLPFC and OFC, which have been among the areas that have been activated during SDLT performance, are the two areas that are significantly related to aspects of executive functions (11).

The main shortcoming of this study was the consideration of an additional important factor central to the subjects' motor-version of the learning task; a kind of working memory load. The subjects had to maintain representation of an aurally presented digit-sequence and convert it to an appropriate sequence of spatial position on a key-pad and then to corresponding motor output, which may be another strong candidate of processes related to the frontal activation. As the usefulness of the motor-variant of the digit-learning task during the fMRI was evident, additional control experiments must be performed to reveal how the frontal activations are related to such a working memory operation.

The change in activation volumes during two different phases of the learning task is also interesting. It is suggested that further research shall examine direct comparisons of the fMRI signal intensities between the two phases, which will provide further evidence about functioning of the anterior prefrontal cortex.

Nevertheless, the findings of the present study supported the hypothesis that serial digit learning and performance on the motor-SDLT, which was used for assessing this ability, are related to the functioning of the frontal lobes. The reason that previous radiological, nuclear, or electrophysiological mapping studies have not been able to demonstrate frontal lobe involvement may be due to the utilization of inappropriate techniques and approaches. Future research on brain correlates of serial digit learning or position processing may benefit from the techniques that were employed and the protocols that had been developed in the present study, specifically the fMRI technology and motor-SDLT.

References

1. Dempster FN. Memory span: sources of individual and developmental differences. Psychol Bull 1981; 89:63-100.
2. Lezak MD. Neuropsychological Assessment. 3rd ed. New York: Oxford University Press, 1995.
3. Zangwill OL. Clinical tests of memory impairment. Proc Royal Soc Med 1943; 36:576-580.
4. Karakaş S, Yalın A, Irak M, Erzengin ÖU. Digit span changes from puberty to old age for different levels of education. Dev Neuropsychol 2002; 22:423-453.
5. Miller GA. The magical number seven, plus or minus two: some limits on our capacity for processing information. Psychol Rev 1956; 63:81-97.
6. Drachman DA, Arbit J, Memory and the hippocampal complex: is memory a multiple process? Arch Neurol 1966; 15:52-61.
7. Kolb B, Whishaw I. Fundamentals of Human Neuropsychology. New York: W.H. Freeman, 1995.
8. McAndrews MP, Milner B. The frontal cortex and memory for temporal order. Neuropsychologia 1991; 29:849-859.
9. Milner B, Corsi P, Leonard G. Frontal-lobe contribution to recency judgements. Neuropsychologia 1991; 29:601-618.
10. Fuster JM, Proceedings of the human cerebral cortex: from gene to structure and function. Brain Res Bull 2000; 52:331-336.
11. Eslinger PJ, Grattan LM. Altered serial position learning after frontal lobe lesion Neuropsychologia 1994; 32:729-739.
12. May CP, Hasher L, Kane MJ. The role of interference in memory span. Mem Cognit 1999; 27:759-767.
13. Goldman-Rakic PS. Development of cortical circuitry and cognitive functions. Child Dev 1987; 58:601-622.
14. Sabbah P, Simond G, Levrier O, et al. Functional magnetic resonance imaging at 1.5 T during sensorimotor and cognitive task. Eur Neurol 1995; 35:131-136.
15. Turner R, Howseman A, Rees GE, Josephs O, Friston, K. Functional magnetic resonance imaging of the human brain: data acquisition and analysis. Exp Brain Res 1998; 123:5-12.
16. Friston KJ, Williams S, Howard R, et al. Movement-related effects in fMRI time-series. Magn Reson Med 1996; 35:346-355.
17. Karakaş HM, Karakaş S. Learning of serial digits leads to frontal activation in functional magnetic resonance imaging: clinical implications (congress abstract). Int J Psychophysiol 2004; 54:17.
18. Talairach J, Tournoux P. Referentially Oriented Cerebral MRI Anatomy. Stuttgart: Thieme Verlag, 1993.
19. Penington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiat 1996; 37:51-87.
20. Solso R. Cognitive Psychology, 4th ed. Needham Heights: Allyn and Bacon, 1995.