Title

Integral calculus problem solving: An fMRI investigation

Running title

An fMRI investigation on integral calculus

Author affiliation

Frank **Krueger**[A], M. Vittoria **Spampinato**[B], Matteo **Pardini**[C], Sinisa **Pajevic**[D], Jacqueline N. **Wood**[A], George H. **Weiss**[D], Steffen **Landgraf**[E] and Jordan **Grafman**[A]

[A] Cognitive Neuroscience Section, NINDS, Bethesda, Maryland, USA

[B] Department of Radiology, Medical University of South Carolina, Charleston, USA

[C] Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Via De Toni 5, 16132 Genoa, Italy

[D] Mathematical and Statistical Computing Laboratory, Division of Computational Bioscience, Center for Information Technology, Bethesda, Maryland, USA

[E] Université Pierre et Marie Curie, Paris VI, France

Corresponding author

Jordan Grafman, Ph.D.

Cognitive Neuroscience Section

National Institute of Neurological Disorders and Stroke

Bldg. 10, Room 7D43, MSC 1440

National Institutes of Health

Bethesda, Maryland 20892-1440, USA

Phone: 301-496-0220

Fax: 301-480-2909

E-Mail: GrafmanJ@ninds.nih.gov

Manuscript information

Number of characters (including space): 18656

Number of figures and tables: 2/ 1

Abstract

Only a subset of adults acquires specific advanced mathematical skills, such as integral calculus. The representation of more sophisticated mathematical concepts probably evolved from basic number systems; however its neuroanatomical basis is still unknown. Using fMRI, we investigated the neural basis of integral calculus while healthy subjects were engaged in an integration verification task. Solving integrals activated a left-lateralized cortical network including the horizontal intraparietal sulcus, posterior superior parietal lobe, posterior cingulate gyrus, and dorsolateral prefrontal cortex. Our results indicate that solving of more abstract and sophisticated mathematical facts, such as calculus integrals, elicits a pattern of brain activation similar to the cortical network engaged in basic numeric comparison, quantity manipulation, and arithmetic problem solving.

Keywords: arithmetic, mathematics, intraparietal sulcus, superior parietal lobe, dorsolateral prefrontal cortex

Introduction

Over the last decade significant progress has been made in uncovering the neural basis of numerical cognition. Recent evidence from human neuroimaging, primate neurophysiology, and developmental neuropsychology revealed that humans and animals share a system of approximate numerical processing for non-symbolic stimuli [1]. Neuroimaging evidence indicates further that performance in simple and complex arithmetic problem solving might be subserved by a fronto-parietal network [2]. Within the parietal lobe, a functional dissociation exists among three parietal regions (see, for a meta-analysis [2]). The horizontal intraparietal sulcus (HIPS) is systematically activated in all number tasks and probably hosts a central amodal representation of quantity [3,4]. The posterior superior parietal lobe (PSPL) is also activated in tasks requiring number manipulation, but is not specific to the number domain and likely supports attentional orientation to the mental number line [5-7]. Finally, the left angular gyrus (AG) is assumed to mediate the retrieval of overlearned arithmetic facts such as the multiplication table [8,9]. Within the frontal lobe, activation of the dorsolateral prefrontal cortex (DLPFC) has been interpreted as a more supportive and general role in the calculation process by sequential ordering of operations, control over their execution, and inhibiting verbal responses [4,10].

Whereas basic numerical or simple arithmetic problem solving, such as mathematical thinking [11], calculation experts [12], complex calculation [13], and training on calculation problems [8], have been frequently investigated, comparatively less is known about the cortical areas involved in solving more abstract and sophisticated mathematical equations such as those used in integral calculus. Using fMRI, we employed a block

design to investigate the neural basis of integral calculus problem solving while healthy subjects were presented with calculus integral problems along with a candidate answer on a computer screen. Subjects were asked to solve each problem mentally and to verify whether the given solution was correct. Before the fMRI experiment, subjects were trained to successfully apply the rules of integral calculus. We assumed that subjects would reduce the task components to basic mathematical skills even though they were solving sophisticated mathematical problems. Therefore, we expected that calculus integral problem solving would most likely engage the same neural networks involved in basic arithmetic problem solving.

Materials and Methods

Subjects. Eighteen right-handed healthy volunteers (thirteen males, age 25.3±3.6 years, education level 17.2±3.2 years) participated in the fMRI experiment, who where native English speakers and had taken at least one calculus course at a college level. All subjects had no history of medical, psychiatric, or neurological diagnoses, and were not taking medication. Informed consent was obtained according to procedures approved by the NINDS Institutional Review Board.

Stimuli. As no prior data was available on the neural correlates of solving integrals, we focused our attention on basic integral calculus problems similar to previous fMRI studies that investigated the neural correlates of simple mathematical tasks (e.g., multiplications). Subjects were asked to solve 48 table integrals by substitution or simplification of the integrand (Fig. 1a).

Procedure. A training session was conducted prior to scanning to insure a similar level of expertise on the task. During the training session, the integrals were presented on a computer screen in a random order across subjects. Subjects were asked to solve the integrals on scratch paper. At the end of the first session, one of the authors reviewed subjects' answers. If necessary, subjects were provided with a list of integrals for which they gave incorrect solutions and were asked to solve them again on scratch paper. At this time, if needed, subjects could consult a list of "table integrals" demonstrating basic integration rules. After all integrals were solved correctly, the training session was repeated for a second time. Note that the solution times for each integral were recorded for both training sessions.

After the training sessions, we employed a block fMRI design that included an experimental and a control condition. For the experimental condition (integration verification task, IVT), an integration problem was presented along with a candidate answer on a computer screen. Subjects were instructed first to solve each problem mentally and then to verify whether the given solution was correct or not. For the control condition (font verification task, FVT), the same integration problem was presented along with a candidate answer. This time, however, subjects were asked to evaluate whether both integrand and solution were displayed in the same or different typefaces (Times New Roman vs. Typewriter). Subjects pressed assigned keys on a response box, for which half of the subjects used their index and middle finger, and the other half responded in the opposite way.

The fMRI experiment consisted of four runs, for which each run was comprised of 8 blocks alternating between blocks of the IVT (n=4) and blocks of the FVT (n=4) (Fig.

1b). Each block lasted 26s, with the first 0.5s of each block used to inform subjects about the upcoming task either “Integrate” for the IVT or “Font” for the FVT. The remaining 25.5s for the experimental task included 3 trials. For each trial, a stimulus was presented for 6.5s followed by an interstimulus interval of 2s, giving a total trial duration of 8.5s. Between blocks, a fixation cross was displayed for 4s. The orders of blocks, runs, and trials were counterbalanced across subjects.

The experiment consisted of 96 trials and the same set of stimuli was used for the IVT (n=48) and FVT (n=48). As the stimuli were identical in both conditions, the FVT controlled for many of the non-mathematical skills required by IVT, such as a motor response, visuo-spatial processing, and orthographic processes. Subjects were asked to respond as quickly and accurately as possible, and response time and error rate were collected during the experiment. After the experiment, subjects were asked to rate how often they used the following strategies on a 7-point Likert scale (1=not at all and 7=on every trial): recall from memory, integration by substitution, integration by parts, and other manipulation. In case of ‘other manipulations’ selected, subjects’ answers were recorded in detail. Finally, subjects were asked to describe in detail how they would solve two provided example integrals.

Image acquisition. Stimulus presentation was synchronized with the scanner pulses using the SuperLab (Cedrus Corporation, http://www.cedrus.com) software package. Prior to scanning, subjects were also trained on a separate set of stimuli to familiarize them with the timing and structure of the tasks. Imaging was performed on a 1.5 T GE whole-body scanner equipped with a standard circularly polarized head coil. FMRI was performed using a T2*-weighted 2D gradient EPI sequence (TR, 2s; TE, 40ms; flip angle, 90°;

thickness, 6mm; number of slices, 22; field of view, 240mm; in-plane resolution, 3.75x3.75mm^2). Per run 420 volumes images were taken parallel to the AC-PC line. The first four volumes in each run were discarded to allow for T1 equilibration effects. Using a 3D SPGR sequence, whole-brain high resolution anatomical images of 124 contiguous slices were also obtained (slice thickness=1.5mm, in-plane resolution=.9375x.9375mm^2).

Image analysis. Imaging analyses were performed using the SPM2 toolbox (Welcome Dept. London, http://www.fil.ion.ucl.ac.uk/spm/). The following data pre-processing steps were applied: slice time correction (sinc interpolation), normalization to standard stereotactic space, high-pass filtering (128s cut-off period), correction for autocorrelation, and spatial smoothing (8mm FWHM). Stereotactic MNI coordinates were translated into standard Talairach space following non-linear transformations [14]. At the single subject level, voxel-wise fixed effect contrast analyses were performed followed by random effect analyses at the group level using a general linear model to create SPM contrast maps [15]. Two predictors were created, one predictor for the IVT and one for the FVT, which were convolved with a boxcar function. By subtracting haemodynamic responses in the font condition from the integration condition, we intended to extract neural responses associated with arithmetic integration processing. Voxels were considered to be significantly activated when they passed false discovery rate correction for multiple comparisons q(FDR)<.05 with more than 10 voxels (3x3x3mm^3) [16].

Results

The response times (RTs) in the fMRI experiment correlated significantly with the solution times in the first (r=.31; p<.035) and second training (r=.50; p<.001) session

outside the scanner; indicating the more time subjects needed to solve an integral in the fMRI experiment, the more time they also needed to solve the same integral on scratch paper in the training sessions. Second, the RTs between FVT and IVT differed significantly (FVT, means±s.d.: 3032±674ms; IVT: 3517±361ms; $t(17)=-2.83$; $p<.012$), whereas the error rates (ERs) did not (FVT: 7.7±5.1%; IVT: 8.0±6.4%; $t(17)=-0.218$; $p=.382$). The RTs and ERs between tasks with a candidate answer that was either correct or incorrect did not differ for IVT [RT: $t(17)=-0.57$; $p<.575$; ER: $t(17)=-1.54$; $p=.142$] and FVT [RT: $t(17)=0.781$; $p=-.446$; ER: $t(17)=-1.4$; $p=.182$]. Finally, subjects reported that they did not prefer any particular problem solving strategy (means±s.e.m.): recall from memory (3.28±0.42); integration by substitution (2.94±0.42); integration by parts (2.22±0.45); and other manipulation (2.55±0.38) in the debriefing session ($F(3,51)=1.23$, $p=.309$).

(Insert Table 1 and Figure 1 about here)

Analysis of fMRI results revealed that contrasting the font condition from the integration condition yielded activations in a left-lateralized cortical network including the IPS, PSPL, precuneus (PC), posterior cingulate gyrus (PCG), and DLPFC (Tab. 1, Fig. 2). No significant brain activation was observed for the inverse contrast.

(Insert Figure 2 about here)

Discussion

The present study explored the neural correlates of integral calculus problem solving. Our results demonstrated that solving integrals activates a left-lateralized cortical network including the IPS, PSPL, PC, PCG, and DLPFC; an activation pattern similar to the

cortical network involved in understanding simple quantities and processing elements of basic calculation [17].

Calculus problem solving is a complex procedure involving calculus-specific skills and non-specific processes such as attention and visuo-spatial processing. Recent research has shown that three parietal regions (HIPS, PSPL, and AG) are engaged in simple and complex arithmetic problem solving [2]. Solving integrals also activated the left HIPS, a region that is systematically activated whenever numbers are manipulated, independently of number notation, and with increasing activation as the tasks put greater emphasis on quantity processing [2]. Volumetric studies have shown that a regional loss of gray matter in the depth of HIPS is characterized by developmental dyscalculia [18,19]. The HIPS has been dissociated from regions of the left parietal lobe involved in finger movements, phoneme detection, saccades or shifting visual attention [20]. Other posterior cortical regions such as the PSPL, PC, and PCG, assist the HIPS in the non-specific cognitive components of calculation by implementing attention-orienting and visuo-spatial processing [21].

Solving integrals further activated the PSPL with a mesial extension into the precuneus, a region that plays a central role in a variety of visuo-spatial tasks [22] and is engaged in tasks requiring number manipulation [5,6]. However, the PSPL is not specific to the number domain and rather supports attentional orientation on the mental number line [2]. Interestingly, calculating integrals did not activate the left AG. Recent neuroimaging studies have demonstrated that the left AG shows greater activation for operations that require access to simple arithmetic facts such as multiplication tables and small exact addition facts [7,20]. The calculation of integrals did not place strong

demands on rote verbal memory. Instead, term simplification and rule application for successful quantity manipulation are required. This conclusion is confirmed by the minimal recruitment of the AG and the strong recruitment of the DLPFC during calculus integral problem solving.

Besides the selection of an appropriate solution algorithm, calculating integrals requires the storage and updating of arithmetic operations. Solving calculus integrals also activated the left DLPFC compatible with the finding that numerosity is first computed in the parietal cortex, then transmitted and kept online by DLPFC activity for further operations [23]. The activation of left DLPFC is strongly associated with planning, ordering serial procedures and controlling their implementation, and in the representation of processes where there is a strong sequential dependence between single contiguous events [24] as required in the multi-step rigorous procedure of calculus integration. For example, signal modifications in the DLPFC were recently observed during the serial subtraction of prime numbers [25].

In summary, the present study demonstrates that solving calculus integrals evoked a pattern of fronto-parietal brain activations similar to the cortical network involved in understanding simple quantities and processing elements of basic calculation. Our analyses suggest that solving of more sophisticated mathematical concepts such as integral calculus involves both the application of solution algorithms and basic calculations. Subjects reported after the experiment, when they were asked to describe in detail how they would solve example integrals, that they first applied rule knowledge how to solve the integral and then performed basic calculation. For example, to integrate $x^2/3$ one has to recall the appropriate solution algorithm, i.e. to add 1 to the exponent of

the numerator of the fraction and then to divide this number by the denominator 3. Therefore, solving integrals activate the HIPS engaged in number manipulation, the PSPL in non-specific calculation processes such as attention and visuo-spatial processing, and the DLPFC in sequential ordering and updating of arithmetic operations.

There are some important technical and methodological issues that deserve discussion. First, interpretation of our findings is limited due to the use of a block design. Given the novelty of our task, we decided to employ a block design, since this design is powerful for assessing BOLD signal magnitude differences between conditions, helping us to explore the underlying network of integral calculus problem solving. However, such a design does not permit the separation of haemodynamic responses for individual trials. For example, it does not allow for a correlation analysis between behavioral measures and brain activations. Future studies, applying event-related fMRI designs, are needed to address such questions to confirm that the observed patterns of brain activation are specific to calculus problem solving.

Second, although our experimental and control task were matched for many of the non-mathematical skills required by the integration task such as motor response, visuo-spatial processing, and orthographic processes, they were not matched in terms of cognitive load. Future imaging studies might compare brain activation not only during an integration condition but also during performing a simple calculation task matched in task difficulty. Comparison of patterns of brain activation associated with integration and a basic calculation task (e.g., multiplication) would be desirable to understand, in more detail, the cognitive differences and similarities of simple and advanced calculation.

Third, it could be argued that subjects did not actually calculate the integrals, but simply memorized the solutions for the 48 integrals that they were exposed to before the fMRI experiment. If this was the case, our results could be an expression of episodic memory retrieval as opposed to actual calculation. We decided to train all subjects to bring them to the same level of familiarity with basic integration rules and their manipulation to account for different levels of calculus expertise and general problem difficulty. However, subjects only solved each problem on scratch paper and were not presented with a list of correct solutions for the problems used in the upcoming fMRI experiment that they could easily memorize. Since subjects reported that they did not favor the "recalling from memory" strategy compared to the other solving strategies and the response times in the fMRI experiment correlated significantly with the solution times in both training sessions, we argue that subjects actually calculated the integrals during the experimental session in the scanner and did not simply retrieve the integral solutions from episodic memory.

Finally**,** it could be argued that the observed activation patterns can be partially accounted for by the process of comparing integrand and possible solutions. Given the need to monitor subjects' performance in a block-design fMRI experiment, we decided to display integrals and possible solutions at the same time. Subjects were instructed first to mentally solve the integral (by processing a specific integration rule or table integral and manipulate the integrands) and then to compare their answer with the given correct or incorrect integral solution. The incorrect solutions were designed to be plausible and close to the correct answers if subjects limited their assessment to simple inspection. Moreover, the solution times and error rates between trials with correct and incorrect

candidate answers did not differ for the integration task, demonstrating that subjects actually calculated the integrals and did not just simply compare integrand and possible solutions.

Conclusion

The present study is the first evidence, to our knowledge, indicating that retrieval of more abstract and sophisticated mathematical facts such as calculus facts, elicits a pattern of brain activation similar to the cortical network involved in understanding simple quantities and processing elements of basic calculation.

Acknowledgments

The authors are grateful to Eric Wassermann for his help with performing the neurological exams and Douglas Hamilton for his help with the illustrations. This research was supported by the Intramural Research Program of the NIH/NINDS/CNS.

References

1. Dehaene S, Molko N, Cohen L, Wilson AJ. Arithmetic and the brain. **Curr Opin Neurobiol** 2004; 14(2):218-224.
2. Dehaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. **Cognitive Neuropsychology** 2003; 20(3/4/5/6):487-506.
3. Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkin S. Sources of mathematical thinking: Behavioral and brain-imaging evidence. **Science** 1999; 284:970-974.
4. Rickard TC, Romero SG, Basso G, Wharton C, Flitman S, Grafman J. The calculating brain: an fMRI study. **Neuropsychologia** 2000; 38(3):325-335.
5. Pesenti M, Thioux M, Seron X, De Volder A. Neuroanatomical substrates of arabic number processing, numerical comparison, and simple addition: a PET study. **J Cogn Neurosci** 2000; 12(3):461-479.
6. Piazza M, Mechelli A, Butterworth B, Price CJ. Are subitizing counting implemented as seperate or functionally overlapping processes? **Neuroimage** 2000; 15:435-446.
7. Menon V, Rivera SM, White CD, Glover GH, Reiss AL. Dissociating prefrontal and parietal cortex activation during arithmetic processing. **Neuroimage** 2000; 12(4):357-365.
8. Delazer M, Domahs F, Lochy A, Bartha L, Brenneis C, Trieb T. The acquisition of arithmetic knowledge - an FMRI study. **Cortex** 2004; 40(1):166-167.
9. Levy LM, Reis IL, Grafman J. Metabolic abnormalities detected by 1H-MRS in dyscalculia and dysgraphia. **Neurology** 1999; 53(3):639-641.
10. Kazui H, Kitagaki H, Mori E. Cortical activation during retrieval of arithmetical facts and actual calculation: a functional magnetic resonance imaging study. **Psychiatry Clin Neurosci** 2000; 54(4):479-485.
11. Sohn MH, Goode A, Koedinger KR, et al. Behavioral equivalence, but not neural equivalence--neural evidence of alternative strategies in mathematical thinking. **Nat Neurosci** 2004; 7(11):1193-1194.
12. Pesenti M, Zago L, Crivello F, et al. Mental calculation in a prodigy is sustained by right prefrontal and medial temporal areas. **Nat Neurosci** 2001; 4(1):103-107.
13. Zago L, Pesenti M, Mellet E, Crivello F, Mazoyer B, Tzourio-Mazoyer N. Neural correlates of simple and complex mental calculation. **Neuroimage** 2001; 13(2):314-327.
14. Talairach J, Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. Thieme Medical Publishers: New York, 1988.

15. Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? **NeuroImage** 1999; 10:1-5.
16. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. **Neuroimage** 2002; 15(4):870-878.
17. Dehaene S, Tzourio N, Frak V, et al. Cerebral activations during number multiplication and comparison: a PET study. **Neuropsychologia** 1996; 34(11):1097-1106.
18. Molko N, Cachia, A., Riviere, D., Mangin, J.F., Bruandet, M., Le Bihan, D., Cohen, L., Dehaene, S. Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. **Neuron** 2003; 40:847-858.
19. Grafman J, Krueger F. Disorders of mathematics: Implications for adult functioning. In Adult Learning Disorders: Contemporary Issues. Lorraine E, Schreiber LE, Wasserstein J, (editors). New York: Neuropsychology Handbooks; in press.
20. Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. **Neuron** 2002; 33(3):475-487.
21. Schmidt D, Krause BJ, Weiss PH, et al. Visuospatial working memory and changes of the point of view in 3D space. **Neuroimage** 2007; 36(3):955-968.
22. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. **Nat Neurosci** 2000; 3(3):292-297.
23. Nieder A, Freedman DJ, Miller EK. Representation of the quantity of visual items in the primate prefrontal cortex. **Science** 2002; 297(5587):1708-1711.
24. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. **Annu. Rev. Neurosci.** 2001; 24:167-202.
25. Burbaud P, Degreze P, Lafon P, et al. Lateralization of prefrontal activation during internal mental calculation: a functional magnetic resonance imaging study. **J Neurophysiol** 1995; 74(5):2194-2200.

Figure legends

Figure 1 (a) Basic table integrals used in the integral calculus experiment* (b) Schematic timeline for integration verification task and font verification task during the fMRI experiment

*A complete list of the integrals with correct and wrong solution is available from the researchers upon request.

Figure 2 Cortical network engaged in integral calculus problem solving (Color bar indicates z-value)

Figure 1

(A) Example integrals

$$\int x^n dx = \frac{x^{n+1}}{n+1} (n \neq -1)$$

$$\int \frac{dx}{x} = \ln x$$

$$\int e^x dx = e^x$$

$$\int a^x dx = \frac{a^x}{\ln a}$$

$$\int \sin x dx = -\cos x$$

$$\int \cos x dx = \sin x$$

$$\int \frac{dx}{1+x^2} = \arctan x$$

(B) fMRI experiment

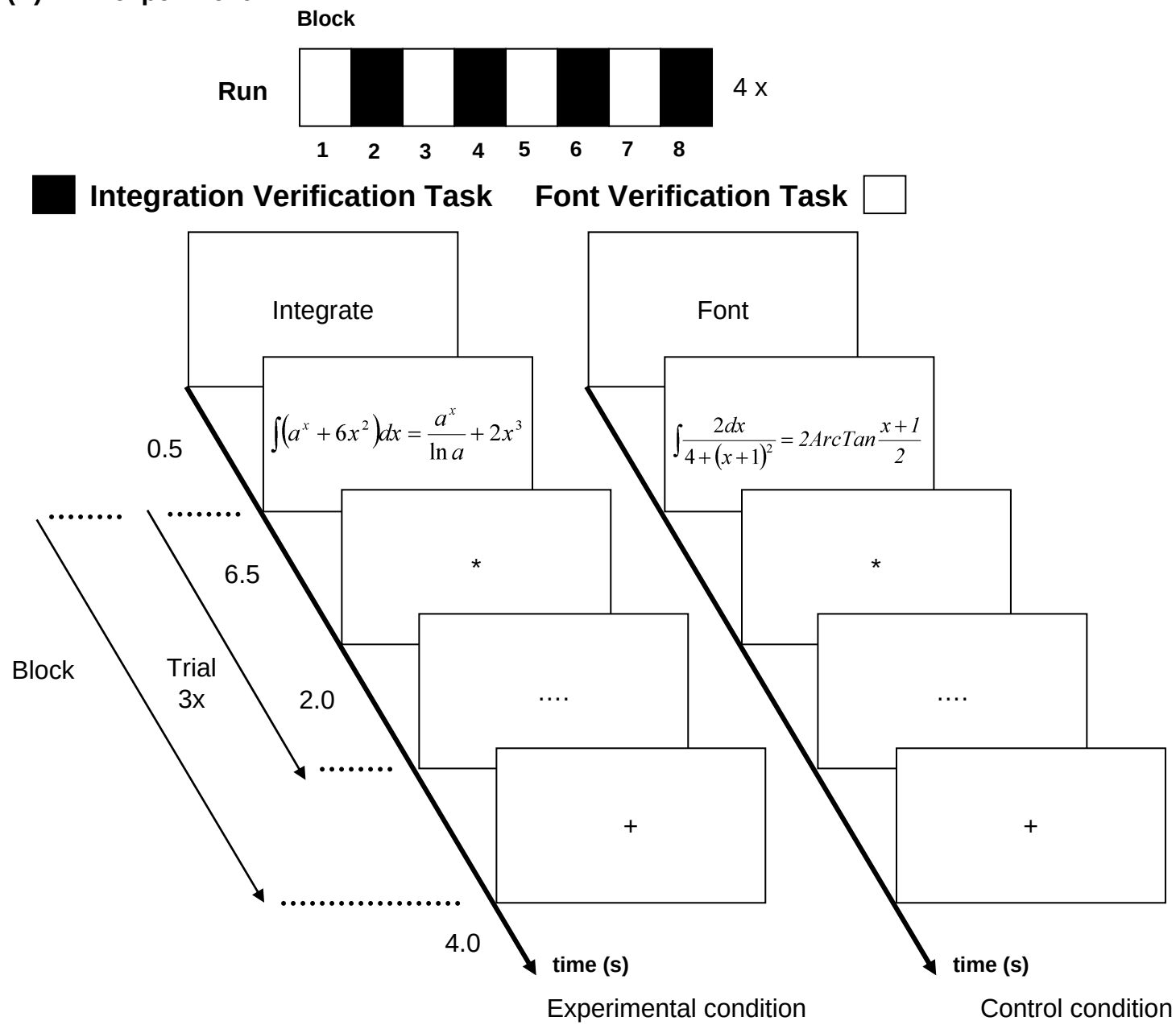

Figure 2

Table 1 Brain areas activated for calculus integral problem solving decisions

Brain Region	Talairach			z score	q(FDR)*
	x	y	z		
L Inferior parietal sulcus (BA 40)	-44	-56	43	4.29	0.008
L Dorsolateral prefrontal cortex (BA 46)	-40	14	43	4.92	0.003
	-28	14	51	4.07	0.012
	-48	21	28	3.99	0.014
L Posterior superior parietal lobe (BA 7)	-8	-71	59	3.55	0.023
	-36	-71	48	4.55	0.006
L & R Precuneus (BA 7 & 9)	-8	-72	37	4.89	0.003
	40	-72	37	3.85	0.016
	-32	-80	41	4.55	0.006
L Posterior cingulate (BA 23 & 31)	0	-33	35	3.45	0.026
	-4	-38	20	3.22	0.039
	-4	-30	24	3.22	0.039

Brodmann's areas (BA) are depicted in parentheses. The stereotaxic coordinates of the peak voxel of the activation are given in Talairach space. Laterality (right and left hemisphere) and z scores are also given.

*q(FDR)<.05 with more than 10 voxels (3x3x3mm^3)