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Neural correlates of counting of sequential sensory and motor events in the human brain

Kenji Kansaku,[a,b] Ari Johnson,[a] Marie-Laure Grillon,[b] Gaëtan Garraux,[a]
Norihiro Sadato,[b] and Mark Hallett[a,*]

[a]*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 5N226, 10 Center Drive MSC 1428, Bethesda, MD 20892-1428, USA*
[b]*Division of Cerebral Integration, National Institute for Physiological Sciences, National Institutes of Natural Sciences, Okazaki 444-8585, Japan*

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Little is known about the ability to enumerate small numbers of successive stimuli and movements. It is possible that there exist neural substrates that are consistently recruited both to count sensory stimuli from different modalities and for counting movements executed by different effectors. Here, we identify a network of areas that was involved in enumerating small numbers of auditory, visual, and somatosensory stimuli, and in enumerating sequential movements of hands and feet, in the bilateral premotor cortex, presupplementary motor area, posterior temporal cortex, and thalamus. The most significant consistent activation across sensory and motor counting conditions was found in the lateral premotor cortex. Lateral premotor activation was not dependent on movement preparation, stimulus presentation timing, or number word verbalization. Movement counting, but not sensory counting, activated the anterior parietal cortex. This anterior parietal area may correspond to an area recruited for movement counting identified by recent single-neuron studies in monkeys. These results suggest that overlapping but not identical networks of areas are involved in counting sequences of sensory stimuli and sequences of movements in the human brain.

Introduction

Few concepts are so universal as numbers. Humans use numbers in so many different contexts, and for so many different functions, that identifying the neural basis of human numerical ability has proved both fascinating and daunting for researchers. One of the most fundamental numerical abilities is “counting”, and we can easily and precisely enumerate small numbers of stimuli from different senses and small numbers of movements from different body parts. Do human adults recruit overlapping neural substrates to count stimuli from different modalities and movements from different effectors, or are distinct neural areas recruited for counting stimuli and movements? This study applied functional magnetic resonance imaging (fMRI) to explore this question.

Considerable evidence suggests that adult humans share some fundamental numerical abilities with infants and animals, particularly the ability to enumerate small numbers of stimuli and events (Feigenson et al., 2004; Fias and Verguts, 2004; Gelman and Butterworth, 2005). Several models for this shared ability have been proposed. There is some significant evidence that both humans and animals have some approximate non-verbal representation of magnitude based on Meck and Church’s accumulator model, in which numerical representation becomes noisier and less reliable with larger numbers, in a linear manner consistent with Weber’s law (Meck and Church, 1983). It is reported that human infants and some animal species have approximately discriminated large magnitudes in a manner consistent with this model (Gallistel and Gelman, 2000); however, infants and animals can also precisely enumerate small numbers up to four and not above four, in ways that cannot be explained by the accumulator model or Weber’s law (Starkey and Cooper, 1980; Hauser et al., 2000; Xu and Spelke, 2000).

Adult humans do appear to enumerate small sets of up to 4 stimuli differently than they enumerate more than 4 stimuli. Visual object enumeration up to 4 stimuli is fast (50–100 ms), facile, and accurate, whereas enumerating greater than 4 stimuli is slower (250–350 ms) and more error prone (Atkinson et al., 1976; Trick and Pylyshyn, 1994). This difference led to a proposed distinction between “subitizing” the enumeration of quantities up to 4 with a rapid, accurate, and confident way, and “counting” numbers greater than 4 (Trick and Pylyshyn, 1994).

Two neuroimaging studies have explored neural correlates of enumerating small numbers in the human brain (Sathian et al., 1999; Piazza et al., 2002). Sathian et al. presented a visual search

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* Corresponding author. Fax: +1 301 480 2286.
E-mail address: hallettm@ninds.nih.gov (M. Hallett).
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type of display, consisting of 16 bars, containing 1–4 (subitizing) and 5–8 (counting) vertical bars, to be enumerated. The subitizing process activated occipital extrastriate cortices, whereas activation during counting process was more widespread in the bilateral posterior parietal cortices and the right inferior frontal cortex. They suggested that the subitizing process uses a preattentive network, whereas counting requires shifts of visual attention. Piazza et al. presented a visual array of 1–4 (subitizing) and 6–9 (counting) dots, and demonstrated increased activations in the occipitoparietal cortices during the counting task compared to activation during the subitizing task. These two previous studies investigated a visuospatial aspect of small number enumeration. In addition to the fact that we can easily count a spatial array of objects, we can also easily manipulate small numbers of objects presented in time. Wynn (1992) showed that infants had numerical competence in dealing with the sequence of events. Neural substrates may exist that characterize the temporal aspect of small number enumeration; however, such mechanisms have not yet been investigated in imaging the human brain. When we count successive events, we can count not only in the visual modality, but also in other sensory modalities, such as auditory and somatosensory. A shared number representation may exist between different sensory modality inputs, and some supporting evidence for this possibility has been provided in monkeys (Jordan et al., 2005), human infants (Starkey et al., 1990), and human adults (Barth et al., 2003).

When we count successive events, we can count not only sensory stimuli but also movements. The single-neuron correlates of these basic numerical abilities have begun to be unraveled in monkey electrophysiology studies (Nieder, 2005), and a recent study has reported single-neuron correlates of movement counting (Sawamura et al., 2002). However, although neuronal mechanisms of sequential movements in adult humans have been extensively investigated (Roland et al., 1980; Sadato et al., 1996; Catalan et al., 1998; Grafton et al., 1998; Garraux et al., 2005; Kansaku et al., 2005), the human neural correlates of movement counting have not been well investigated.

Behavioral studies have begun to suggest the possibility of neural substrates consistently recruited for sensory and motor counting, but the extent of this has not yet been investigated. In this study, we specifically investigated the neural correlates of counting small numbers of successive sensory and motor events. In doing so, we seek a foundation upon which to understand how human numerical abilities have developed. In particular, the aim of this study is to investigate how the neuronal networks for enumerating a small number of sensory stimuli and movements are segregated and/or overlapped. This study investigates the neural network that adult humans use to count sets of 2, 3, or 4 sequential sensory stimuli or movements. To reveal brain regions consistently activated in both sensory and motor enumeration of small numbers, the study aims to identify areas that are involved in counting across multiple sensory modalities and multiple movement effectors. Using an event-related paradigm, this experiment identified areas activated in: (1) counting sensory stimuli across visual, auditory, and somatosensory modalities, (2) motor counting independent of the body part executing the movement, and (3) both sensory and motor counting (Experiment 1). To determine that areas activated in both sensory and motor counting were explicitly involved in sensory counting and not simply preparing response movements, we performed a control experiment (Experiment 2). We also performed an additional set of experiments to determine whether counting activations in Experiment 1 were dependent upon stimulus presentation timing, basic modality detection processes, or number word verbalization (Experiment 3).

Materials and methods

Subjects

We studied a total of 31 healthy volunteers; 12 subjects, 8 males (age 22–50 years) and 4 females (age 23–33 years) in Experiment 1; 6 subjects, 2 males (age 32 years) and 4 females (age 26–46 years) in Experiment 2; and 13 subjects, 7 males (20–35 years) and 6 females (26–30 years) in Experiment 3. Each individual subject participated in one of the experiments and there was no overlapped participation between different experiments. All subjects were neurologically normal and strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971). The studies received approval from the Institutional Review Boards. All subjects gave written informed consent according to institutional guidelines.

Experimental design

Experiments 1–2

Event-related fMRI study design was applied in this study. In Experiments 1 and 2, three sensory modalities were studied in three separate sessions: visual (white rectangle), auditory (beeping sound), and somatosensory (air-puff). We presented a sequence of 2, 3, or 4 sensory stimuli, with 300 ms durations, separated by 200 ms interstimulus intervals, and asked subjects to count the number of sensory stimuli. Similar events were repeated 20 times in one session. In Experiment 1, we presented a small white circle response cue 12.5s later than the presentation of the stimuli, and asked the subjects to indicate the number of stimuli they felt by tapping a touch pad the corresponding number of times (Fig. 1A). In each separate session of visual, auditory, and somatosensory stimuli, three types of effectors (left hand, right foot, and right hand) were associated with each input stimulus respectively, and performed the tapping movements by the effector. Middle fingers were used for hand movements; the big toe was used for foot movements. An MR compatible foot-rest was used to stabilize the subjects’ feet, and the subjects were instructed to touch the response pad placed on the foot-rest by their toe, keeping their head as still as possible. A bite bar system was used to minimize subjects’ head movements. In Experiment 2, visual, auditory, and somatosensory stimuli identical to those used in Experiment 1 were used, but the subjects were not instructed to make any output movements related to the sensory stimuli (Fig. 2A). This experiment was added because we wanted to make sure the activation pattern observed in the first imaging experiment did not require motor preparation. The order of the experimental sessions was balanced among the subjects, within Experiments 1 and 2.

Experiment 3

In Experiment 3, we prepared a task that had 40 sets of sequential stimuli consisting of visual (white rectangle), auditory (beeping sound), or somatosensory (air-puff) stimuli (Fig. 3A). A set of sequential stimuli consisted of one of the sensory modalities, and it had 2, 3, or 4 sensory stimuli of 300 ms duration each, separated by 200 ms interstimulus intervals. The subjects were required to judge the sensory modality of the sequential stimuli

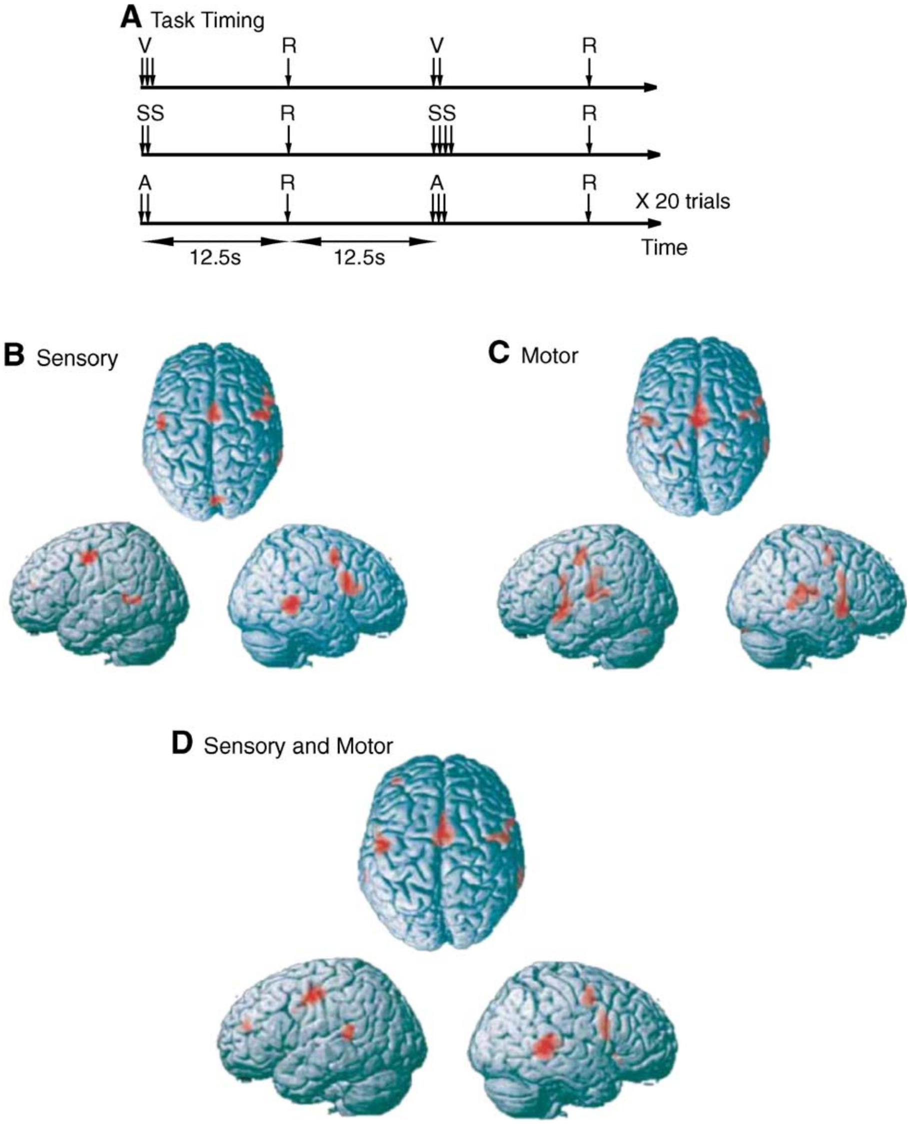

Fig. 1. Timing of conditions for Experiment 1 and spatial distribution of activated areas displayed on template brain. (A) Three types of modalities were applied in three separate sessions: visual (white rectangle, V), auditory (beeps, A), and somatosensory (air-puff, SS). We presented a sequence of 2, 3, or 4 sensory stimuli, of 300 ms duration, separated by 200 ms interstimulus intervals, and asked subjects to count the number of sensory stimuli. After seeing a response cue (white circle, R), the subjects were required to indicate the number of stimuli they felt by tapping a touch pad the corresponding number of times. Left hand, right foot, and right hand were used in the visual, auditory, and somatosensory sessions, respectively. Twenty trials were included in one session. (B) Spatial distribution of the consistent activation displayed on template brain during counting successive stimuli. (C) Spatial distribution of the consistent activation during counted movements. (D) Spatial distribution of the consistent activation during counting sensory stimuli from different modalities and counting movements executed by different effectors. In each figure, red dots represent pixels detected in the conjunction analyses ($P < 0.05$, family-wise error correction for multiple comparisons). Activated pixels located within 15 mm from the surface of the brain are displayed in the color dots. Talairach coordinates (Talairach and Tournoux, 1988) and *t* scores of the activated brain regions are listed in Table 1.

(visual, auditory, or somatosensory) (a Modality Detection task). We then instructed the subjects to count the successive sensory stimuli in a following session (a Counting (Regular) task). Sensory stimuli presented in these tasks were exactly same, but internal processes that the subjects performed were different; i.e., the Counting (Regular) task involved explicit counting process, whereas the Modality Detection task did not. We also prepared a task that had sequential sensory stimuli in irregular rhythms (a Counting (Irregular) task; Fig. 3A). This had 40 sets of sequential stimuli consisted of visual (white rectangle), somatosensory (air-puff), or auditory (beeping sound). A set of sequential stimuli consisted of one of the sensory modalities, and it had 2, 3, or 4 sensory stimuli of 300 ms duration each, separated by varied interstimulus intervals (50 ms–650 ms; mean: 200 ms). In the actual experiment, the Modality Detection task was performed at the beginning of the experiment, and the order of the Counting (Regular) and Counting (Irregular) tasks was randomized among subjects to exclude an order effect. The subjects were required to push response pads by their right fingers, when they saw a white circle response cue presented 12.5 s later than the presentation of the sensory stimuli. Visual, auditory, and somatosensory stimuli were assigned to 2nd, 3rd, and 4th fingers respectively in the

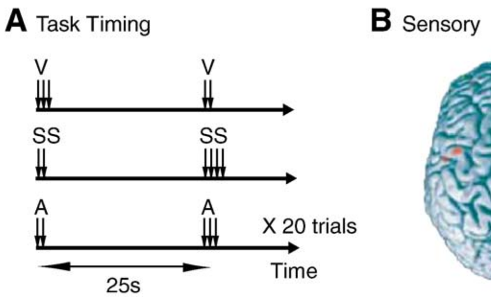

Fig. 2. Timing of conditions for Experiment 2 and spatial distribution of activated areas displayed on template brain. (A) Same sensory stimuli with the Experiment 1 were used, but the subjects were not required to make output movements. (B) Spatial distribution of the consistent activation displayed on template brain during counting successive stimuli. Red dots represent pixels detected in the conjunction analysis ($P < 0.05$, family-wise error correction for multiple comparisons). Activated pixels located within 15 mm from the surface of the brain are displayed in the color dots.

Modality Detection task, and 2, 3, and 4 successive stimuli were assigned to 2nd, 3rd, and 4th fingers respectively in the Counting (Regular) and Counting (Irregular) tasks. The subjects' responses were recorded using a 5 button response system (5 Key response with fiber optic, Resonance Technology, Inc., Northridge, CA).

At the end of the Experiment 3, we included a task paradigm to test whether the premotor activation was related to internal speech. In the task, we presented number words of the small numbers either aurally or visually, then asked the subjects to memorize the number and make an internal speech of the number word when they saw a response cue (Internal Speech task).

Experimental procedures

The experiments were controlled by Presentation software (Neurobehavioral Systems, Inc., San Francisco, CA). For the auditory stimuli, in all experiments, we used a pure tone of 1.5 kHz frequency and approximately 95 dB loudness at the distal end of audio systems. For the visual stimuli, in all experiments, a white rectangle was projected on tangent screens reflected in overhead mirrors; and the visual angles of the rectangle were approximately $6 \times 4°$. For the somatosensory stimuli, air puffs were delivered by an air pump (Vacuum/pressure Station, Barnant Co., Barrington, IL) with a voltage-controlled solenoid valve (Solenoid valve model M310, Humphrey Products Co., Kalamazoo, MI) for controlling the timing and duration of the air puffs in Experiments 1 and 2, by an air pump (Air compressor AC-500, Too Marker Products, Inc., Tokyo, Japan) with a voltage-controlled solenoid valve (Solenoid valve model A2-5201, CKD Co., Aichi, Japan) in Experiment 3. All the stimuli from different modalities were delivered to the head area, the center of the head-centered frame of reference (Duhamel et al., 1997; Graziano and Gandhi, 2000), and the subjects were asked to pay attention to each stimulus. A fixation point was displayed on a tangent screen throughout the experiments to minimize subjects' eye movements. To reduce the machinery noise during scanning, we asked subjects to wear earplugs.

In Experiment 1 and 2, subjects were given the task paradigms the day before the experiments, and a 30-min practice session was conducted prior to the scanning. Subjects were given both written and verbal instructions. In Experiment 3, subjects were given the task paradigm of the Modality Detection task just before the scanning, and a 15-min practice session was conducted. After finishing the Modality Detection task, we instructed the subjects to count the successive stimuli in the following tasks: the Counting (Regular) task and the Counting (Irregular) task.

Imaging

BOLD contrast image volumes (Ogawa et al., 1993) were acquired. In Experiments 1 and 2, MR data were collected on a

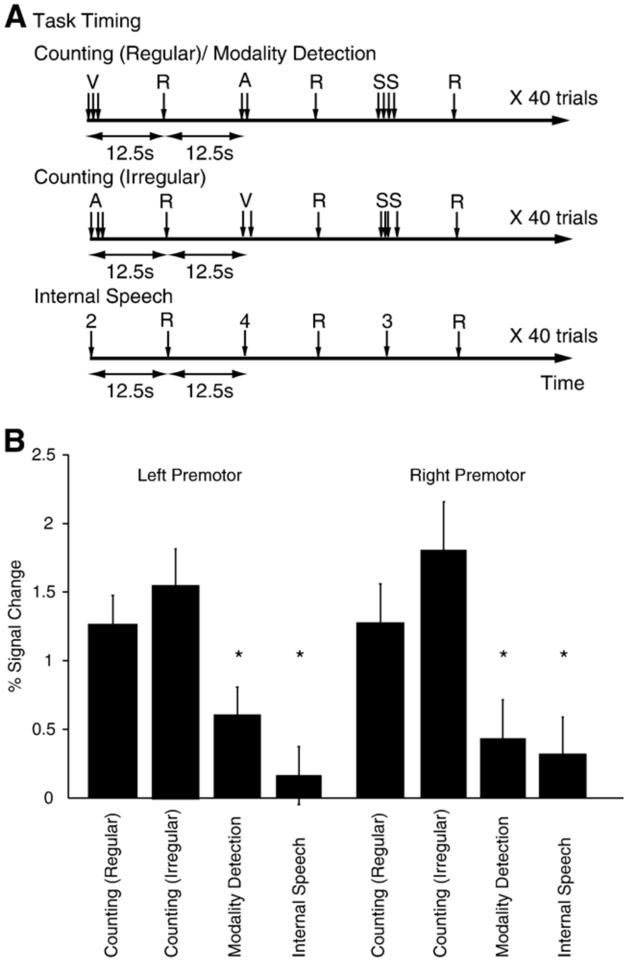

Fig. 3. Timing of tasks and fMRI activation from Experiment 3. (A) Three types of modalities, visual (white rectangle, V), auditory (beeps, A), and somatosensory (air-puff, SS), were applied in each session. In the Modality Detection task and Counting (Regular) task, we presented a sequence of 2, 3, or 4 sensory stimuli, of 300 ms duration, separated by 200 ms interstimulus intervals. In the Counting (Irregular) task, we presented a sequence of 2, 3, or 4 sensory stimuli, of 300 ms duration, separated by randomized interstimulus intervals (50–650 ms; mean: 200 ms). The Modality Detection task was performed first and the subjects were asked to judge the sensory modality that the sequence was composed. Then the subjects were instructed to count the number of sequence in the following Counting (Regular) task and Counting (Irregular) task. At the end of Experiment 3, we added the Internal Speech task, which we presented number words of the small numbers either aurally or visually, then asked the subjects to memorize the number and make an internal speech of the number word when they saw a response cue. (B) The percentage of signal change was calculated individually within spherical volumes of interest with a diameter of 10 mm in the left and right premotor cortices. The fMRI activations in the areas decreased when the subjects did not explicitly count the number of sequential stimuli (*$P < 0.005$, Wilcoxon signed rank test).

3T scanner (Signa, GE Medical Systems, Milwaukee, WI) using gradient-echo echo-planar imaging (TR/TE = 2500 ms/25 ms, FA = 90°, slice thickness/gap = 5/1 mm, FOV = 22 × 22 cm^2, matrix size = 64 × 64, 22 slices). We improved magnetic field homogeneity by using both linear and second order shims. This method was developed in spectroscopic imaging at 1.5 T (Spielman et al., 1998), and the effectiveness of the method for gradient-echo echo-planar imaging was evaluated at 3.0 T (Kansaku et al., 2000). Two hundred sequential images of each slice were collected during each experiment. In Experiment 3, MR data were collected on a 3 T scanner (The Magnetom Allegra, Siemens Co., Erlangen, Germany) using gradient-echo echo-planar imaging (TR/TE = 2500 ms/25 ms, FA = 90°, slice thickness/gap = 5/1 mm, FOV = 22 × 22 cm^2, matrix size = 64 × 64, 28 slices). Four hundred and five sequential images of each slice were collected during each experiment. During the collection of the BOLD contrast image volumes, in all experiments, pulses coming from the MRI scanner were monitored and the experimental sequences were triggered.

Data analysis

Algorithms implemented in statistical parametric mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995) were used in the data analyses. For each individual subject, scans were realigned to the first image and stereotactically normalized to a standard stereotactic space (Montreal Neurological Institute (MNI) brain template). During the spatial normalization process, scans were resampled into voxels that were 2 × 2 × 2 mm in the x (right–left), y (rostral–caudal), and z (dorsal–ventral) directions, respectively. All scans were then smoothed with a Gaussian filter (6 mm full-width at half-maximum, FWHM) to accommodate individual anatomical variability. A hemodynamic response function was used to characterize condition effects. We performed a multiple regression, second-level conjunction analysis based on the minimal statistic (Price and Friston, 1997; Friston et al., 1999, 2005) to find the brain regions consistently activated with the three sensory and the three motor conditions. Significance level was set at a height threshold of $P < 0.05$ with family-wise error correction for multiple comparisons. To report activity, we converted the MNI coordinates into Talairach coordinates (1988) using a linear transformation matrix and listed the Talairach coordinates. It should be noted that a significant conjunction does not mean all the contrasts were individually significant (i.e., a conjunction of significance). It simply means that the contrasts were consistently high and jointly significant. This is equivalent to inferring that one or more effects were present (Friston et al., 2005).

Results

Behavioral data

Subjects' behaviors were recorded in Experiment 1, and mean accuracies in the visual, auditory, and somatosensory stimulus conditions were 97.1%, 96.7%, and 97.0%, respectively. Mean reaction times in the experimental conditions were 628.0 ± 184.5 ms for the visual stimulus condition, 530.2 ± 177.3 ms for the auditory stimulus condition, and 537.3 ± 122.3 ms for the somatosensory stimulus condition.

Subjects' behaviors were also recorded in Experiment 3, and mean accuracies in the Modality Detection, Counting (Regular), and Counting (Irregular) tasks were 98.5%, 95.6%, and 95.1%, respectively. Mean reaction times in the experimental tasks were 225.6 ± 133.4 ms for the Modality Detection task, 193.1 ± 114.2 ms for the Counting (Regular) task, and 192.6 ± 128.9 ms for the Counting (Irregular) task.

Imaging data

Experiment 1

In the first experiment, we presented a sequence of 2, 3, or 4 sensory stimuli of 300 ms duration each, separated by 200 ms interstimulus intervals, and asked subjects to count the number of sensory stimuli. Visual (white rectangle), auditory (beeping sound), and somatosensory (air-puff) stimuli were used in different sessions. Twelve and a half seconds later, after seeing a white circle, subjects were required to indicate the number of stimuli they counted by tapping a touch pad the corresponding number of times using left hand, right hand, and right foot, respectively (Fig. 1A). In an event-related fMRI design, we recognized each sensory or motor counting period as an event, starting from onset from each sequence. Fig. 1B shows the spatial distribution of activation during counting successive stimuli. By applying a conjunction analysis, the most significant consistent sensory activation during counting of multisensory stimuli was observed in the right posterior superior/middle temporal cortex (Fig. 1B, Table 1). Significant sensory activations were also found in the right inferior frontal gyrus, left and right premotor cortex, and medial frontal gyrus. The activated area in the premotor cortices could be between the dorsal and ventral premotor cortex, because there are multimodal neurons in both dorsal and ventral premotor cortex in monkeys. The coordinate of the local maxima observed in the medial frontal gyrus [$x = 0$, $y = 5$, $z = 55$; Talairach coordinate (Talairach and Tournoux, 1988)] was located anterior to the vertical anterior commissure line, and it suggests that the area is in the presupplementary motor area. The right supramarginal gyrus, which includes the intraparietal sulcus, was also activated. In each sensory modality condition, activated areas for counting were distributed in the respective primary, secondary, and associated higher order cortical areas as expected. For example, significant activations were observed in the right occipital lobe for the visual session ($t = 6.95$; $x = 40$, $y = -88$, $z = -4$), the right superior temporal gyrus for the auditory session ($t = 15.83$; $x = 59$, $y = -14$, $z = -3$), and the postcentral gyrus/inferior parietal lobule for the somatosensory session ($t = 3.64$; $x = 59$, $y = -33$, $z = 42$). It is noteworthy that these activations in the primary sensory cortices were not detected to be significant in the results of the conjunction analysis because it is based on the minimal t statistic.

In the second part of the study, we asked subjects to make counted movements with the left hand in the visual stimulus condition, the right foot in the auditory stimulus condition, and the right hand in the somatosensory stimulus condition. By applying a conjunction analysis, the medial frontal gyrus was found to be significantly activated during counted movements executed by different effectors (Fig. 1C, Table 1). The coordinate of the local maxima was located more posteriorly than the area that shows activation during counting of sensory stimuli, and suggests that the area is the supplementary motor area, which has been thought to be important in sequential movements (Tanji, 2001). The right and left thalamus, frontal operculum, and

Table 1
Group analysis of areas of consistent activation in Experiment 1

Brain region (Brodmann's area)	*x*	*y*	*z*	*t* statistic	*P* value
Sensory					
Right posterior superior/middle temporal cortex (BA 22/21)	59	−43	2	6.50	0.000
Right inferior frontal gyrus (BA 9)	48	15	20	5.52	0.000
Left premotor cortex (BA 6/4)	−51	−4	43	5.39	0.000
Medial frontal gyrus (BA 6)	0	5	55	4.58	0.000
Right premotor cortex (BA 6)	50	0	46	4.47	0.000
Cuneus (BA 19)	8	−80	37	3.60	0.000
Left posterior superior/middle temporal cortex (BA 22/21)	−64	−52	6	3.18	0.000
Right anterior insula/frontal operculum	34	25	−6	3.00	0.001
Right supramarginal gyrus (BA 40)	42	−45	35	2.96	0.002
Left anterior middle frontal gyrus (BA 46/10)	−37	49	14	2.66	0.018
Motor					
Medial frontal gyrus (BA 6)	0	−1	52	9.27	0.000
Right thalamus	10	−16	1	6.25	0.000
Left thalamus	−10	−21	−1	5.77	0.000
Left frontal operculum	−42	2	5	5.60	0.000
Left premotor cortex (BA 6/4)	−51	−6	44	5.58	0.000
Right posterior superior temporal cortex (BA 22)	53	−30	16	5.53	0.000
Left inferior postcentral gyrus/parietal operculum (BA 40/7/5)	−59	−20	21	5.47	0.000
Right frontal operculum	59	10	9	5.41	0.000
Right premotor cortex (BA 6)	46	−1	52	4.13	0.000
Cerebellar vermis	2	−67	−19	3.87	0.000
Sensory and motor					
Left premotor cortex (BA 6/4)	−51	−6	44	5.03	0.000
Medial frontal gyrus (BA 6)	0	5	55	4.58	0.000
Right posterior superior/middle temporal cortex (BA 22/21)	59	−41	2	3.92	0.000
Right premotor cortex (BA 6)	48	1	50	3.45	0.000
Right inferior frontal gyrus (BA 44)	55	9	18	2.96	0.000
Left thalamus	−8	−20	−2	2.59	0.000
Right thalamus	8	−17	1	2.56	0.000
Left posterior superior temporal cortex (BA 22)	−51	−38	13	2.50	0.000
Left anterior middle frontal gyrus (BA 46/10)	−38	47	16	2.47	0.000
Right anterior insula/frontal operculum	36	21	−3	2.28	0.000

premotor cortex were also found to be consistently activated. Activations were also observed in the right posterior superior temporal cortex. The left anterior parietal area was found to be additionally activated, and this area could be a human neural correlate to a parietal area involved in enumerating movements in monkeys (Sawamura et al., 2002). In each condition, activated areas for counted movements were distributed in the respective primary or secondary motor areas as expected. For example, significant activations were observed in the right precentral gyrus for left hand movement ($t = 13.19$; $x = 36$, $y = -24$, $z = 55$), the paracentral lobule for right foot movement ($t = 18.00$; $x = -4$, $y = -32$, $z = 64$), and the post/precentral gyrus for right hand movement ($t = 16.77$; $x = x = -38$, $y = -23$, $z = 49$). It is noteworthy that these activations in the primary sensorimotor cortices were not detected in the results of the conjunction analysis.

It is possible that there exist neural substrates consistently activated for counting sensory stimuli from different modalities and for counting movements executed by different effectors. Therefore, we evaluated activation in the sensory motor processing of counting. By applying a conjunction analysis, the most significant consistent activation was observed in the left premotor cortex (Fig. 1D, Table 1). The right premotor cortex also showed consistent activation. Significant activation was also found in the medial frontal gyrus (presupplementary area), and the coordinate of the local maxima ($x = 0$, $y = 5$, $z = 55$) was the same as the coordinate that showed activation during counting of visual, auditory, and somatosensory stimuli (Table 1). The right posterior superior/middle temporal cortex also showed significant sensory and motor activation. Activation in the posterior superior/middle temporal cortex was bilaterally represented, but more significant and widely distributed in the right than the left hemisphere. In addition to these cortical regions, the bilateral thalamus also demonstrated consistent activation (Table 1).

Experiment 2

The most significant consistent activation was observed in the left premotor cortex in Experiment 1 (Fig. 1D). The premotor cortex may have an important role in counting sequential sensory and motor events. However, it is possible that sensory motor activation is a motor-related activity instead of a counting-related activity, because sensory perception is always linked to motor output in Experiment 1's task design. To investigate whether the activations in the premotor cortices observed during counting successive sensory stimuli are truly related to the sensory processing instead of motor-related processing such as motor preparation, an additional experiment was done. In this task paradigm, similar experimental conditions were used, but the subjects were not required to perform any motor responses, and were only asked to count the sensory stimuli without moving (Fig. 2A). Completely naive subjects who had never participated in our studies were recruited in Experiment 2, in order to exclude the possibility that the former experience with the sensory and motor tasks would induce motor-related activity. This additional task paradigm still induced activation in the premotor cortices; left premotor cortex ($t = 5.96$; $x = -46$, $y = 1$, $z = 48$) and right premotor cortex ($t = 3.94$; $x = 48$, $y = -4$, $z = 39$) were observed to be significantly activated during counting successive sensory stimuli ($t > 2.82$, $P < 0.05$, family-wise error correction for multiple comparisons; Fig. 2B).

Experiment 3

Activation in the premotor cortex. These results in Experiment 2 showed that the significant premotor cortex activation observed during counting successive stimuli occurred even in the absence of motor planning. The premotor cortex may have a role in counting successive events. However, the activation still might have been due to other cognitive processes, such as attentional processes to perceive successive events without explicit counting. To address this issue, in the third experiment, we prepared a task that had 40 sets of visual (white rectangle), auditory (beeping sound), or somatosensory (air-puff) sequential stimuli (Fig. 3A). A set of sequential stimuli consisted of one of the sensory modalities, and it had 2, 3, or 4 sensory stimuli of 300 ms duration each, separated by 200 ms interstimulus intervals. We asked the subjects to judge the sensory modality of the sequential stimuli (visual, auditory, or somatosensory) (a Modality Detection task). In this experiment, we again recruited completely naive subjects who had never participated in our studies, and performed this task without giving any information about our counting project. After finishing the task, we made sure that all subjects who participated in this task were aware that the stimuli were coming sequentially, but did not pay attention to how many stimuli there were and did not explicitly count them. We then instructed the subjects to count the successive sensory stimuli in a following session (a Counting (Regular) task), in order to compare the activation in the premotor cortex between the Modality Detection task and the Counting (Regular) task. Sensory stimuli presented in these tasks were exactly same, but internal processes that the subjects performed were different; i.e., the Counting (Regular) task involved explicit counting process, whereas the Modality Detection task did not.

The Counting (Regular) task showed activations in the premotor cortices; left premotor cortex ($t = 4.79$; $x = -46$, $y = 8$, $z = 42$) and right premotor cortex ($t = 4.33$; $x = 42$, $y = 12$, $z = 51$) were observed to be activated ($t > 2.60$, $P < 0.05$, family-wise error correction for multiple comparisons; Table 2). However, in

Table 2
Group analysis of areas of consistent activation in Experiment 3

Brain region (Brodmann's area)	*x*	*y*	*z*	*t* statistic	*P* value
Counting (regular)					
Left premotor cortex (BA 6/8)	−46	8	42	4.79	0.000
Left premotor cortex (BA 6)	−34	4	48	4.71	0.000
Left supramarginal gyrus (BA 40)	−42	−46	48	4.36	0.000
Right posterior superior temporal cortex (BA 22)	59	−48	4	4.34	0.000
Right premotor cortex (BA 6)	42	12	51	4.33	0.000
Medial frontal gyrus (BA 6)	−2	14	55	3.20	0.001
Counting (irregular)					
Right inferior frontal gyrus (BA 9)	53	21	25	7.68	0.000
Right premotor cortex (BA 6)	40	12	51	4.74	0.000
Medial frontal gyrus (BA 6)	0	12	51	7.20	0.000
Left premotor cortex (BA 6)	−34	4	48	5.55	0.000
Precuneus (BA 7)	−10	−74	44	5.51	0.000
Right posterior superior/middle temporal cortex (BA 22)	61	−51	−1	5.04	0.000
Left cerebellum	−10	−77	−21	4.16	0.000
Right posterior parietal cortex (BA7)	42	−62	51	3.42	0.000
Left posterior parietal cortex (BA7)	−34	−56	45	3.81	0.000
Modality detection					
Right posterior superior/middle temporal cortex (BA 22)	63	−44	4	3.94	0.000
Precuneus (BA 7)	10	−71	50	3.33	0.000

the Modality Detection task, although there were significant activations in the right posterior superior/middle temporal cortex and precuneus, no significant activated cluster was detected in the premotor cortices (Table 2). The percentage of signal change was calculated individually within spherical volumes of interest in the left and right premotor cortices, and it was confirmed that the premotor activation was significantly greater during the Counting (Regular) task than during the Modality Detection task in both left premotor cortex ($P = 0.003$) and right premotor cortex ($P = 0.0008$, Wilcoxon signed rank test; Fig. 3B).

The activation still might have been due to the other non-numerical parameters that co-vary with number, such as rhythm. Therefore, we added another control task, aiming to investigate whether the premotor cortex activations during counting is specific to the regular presentation of the sequential stimuli. We presented the sequential stimuli in irregular rhythms in this control task (a Counting (Irregular) task; Fig. 3A). We prepared a task that had 40 sets of visual (white rectangle), somatosensory (air-puff), or auditory (beeping sound) sequential stimuli. A set of sequential stimuli consisted of one of the sensory modalities, and it had 2, 3, or 4 sensory stimuli of 300 ms duration each, separated by varied interstimulus intervals (50 ms–650 ms; mean: 200 ms). In the actual experiment, although the Modality Detection task was performed at the beginning of the experiment, the order of the Counting (Regular) and Counting (Irregular) tasks was randomized among subjects. In this Counting (Irregular) task, left premotor cortex ($t = 5.55$; $x = -34$, $y = 4$, $z = 48$) and right premotor cortex ($t = 4.74$; $x = 40$, $y = 12$, $z = 51$) were significantly activated ($t > 2.63$, $P < 0.05$, family-wise error correction for multiple comparisons; Table 2). Similar to the other tasks, the percentage of signal change was calculated individually within spherical volumes of interest in the left and right premotor cortices, and it showed that premotor activation was significantly greater during the Counting (Irregular) task than during the Modality Detection task in both the left premotor cortex ($P = 0.00006$) and the right premotor cortex ($P = 0.000009$, Wilcoxon signed rank test; Fig. 3B). Mean percentage of signal change was bigger in the Counting (Irregular) task than in the Counting (Regular) task, but these were not significant (the left premotor cortex: $P = 0.17$, and the right premotor cortex: $P = 0.07$, Wilcoxon signed rank test). The premotor cortices activated when the subjects counted the successive stimuli, and it did not depend on the regularity in time that the stimuli were composed.

A similar activation pattern with the lateral premotor cortex was observed in the medial premotor cortex: the presupplementary motor area. The area was significantly activated in both Counting (Regular) task ($t = 3.20$; $x = -2$, $y = 14$, $z = 55$) and Counting (Irregular) task ($t = 7.20$; $x = 0$, $y = 12$, $z = 51$), but not in the Modality Detection task.

The results showed that the premotor activation did not depend upon rhythm. However, there still remained a possibility that the activation of the area depends on internal speech of the number words during counting. In Experiment 3, we included an additional task in which number words of the small numbers were presented either aurally or visually; subjects were asked to memorize the number and make an internal speech of the number word when they saw a response cue (Internal Speech task; Fig. 3A). Signal change following the response cue was evaluated as the internal speech activation. The percentage of signal change in the left and right premotor cortices was calculated. The activation was significantly greater during the Counting (Regular) task than during the Internal Speech task in both the left premotor cortex ($P = 0.00001$), and the right premotor cortex ($P = 0.0003$; Fig. 3B), and also significantly greater during the Counting (Irregular) task than during the Internal Speech task in both the left premotor cortex ($P = 0.0000006$) and the right premotor cortex ($P = 0.000006$, Wilcoxon signed rank test; Fig. 3B).

Activation in other brain regions. The experiment also demonstrated task-related activation in areas other than the premotor cortex (Table 2). The posterior parietal cortex showed significant activation in the Counting tasks (Regular and Irregular) but not in the Modality Detection task. The activation was mainly found in the left supramarginal gyrus (Brodmann's area: BA 40) in the Counting (Regular) task, and in the bilateral posterior parietal cortex (BA 7) in the Counting (Irregular) task.

The area that showed activation in the Counting tasks (Regular and Irregular) and the Modality Detection task was the right posterior superior/middle temporal cortex; which suggests that the area participates in a more general role, such as general attention in detecting events.

Discussion

This study aimed to assess whether an overlapping neural network underlies sensory and motor counting processes. The results of these experiments revealed neural networks for sensory and motor counting that are partially overlapping and partially distinct. Counting of successive sensory and motor events appears to recruit a network of areas in the bilateral premotor cortex, presupplementary motor area, posterior temporal cortex, and thalamus. The most significant consistent activation was in the lateral premotor cortex, and its activation was not due to movement preparation, stimulus presentation timing, or number word verbalization. By contrast, distinct parts of the parietal cortex were activated for sensory counting and movement counting. We found that movement counting, but not sensory counting, activated the anterior parietal cortex, and this area appears to be a human neural correlate to a parietal area involved in enumerating movements in monkeys. Sensory counting, but not movement counting, activated the posterior parietal cortex, an area that has previously been implicated in supramodal numerical processing.

Before further discussion of the role of the areas in the context of counting in humans, we should first carefully explore the meaning of the term "counting". Recently, Nieder (2005) suggested that the human's number processing includes three aspects: cardinal, ordinal, and nominal. Nieder's proposal is somewhat similar to an earlier definition of counting by Gelman and Gallistel (1978), which identifies three principal elements: (1) the one-to-one principle, which applies ticks in one-to-one correspondence; (2) the stable order principle, where numbers are represented in a specific sequence; and (3) the cardinal principle, which recognizes that each number includes all the numbers before it. Gallistel and Gelman's description further suggests that the essential elements of counting are not only numerical, and it is necessary for us to face the non-numerical factors to understand the neuronal basis of counting. The nature of numerical competence was also recently described by Gordon, who argued that, "any estimation of a person's numerical competence will always be confounded with performance factors of the task" (Gordon, 2004). We will therefore explore both the possible numerical and non-numerical roles that each activated area may have in counting sequential sensory and motor events.

Role of the premotor cortex in sensory and motor counting

The most significant sensory and motor activation was observed in the left lateral premotor cortex. A related set of studies indicates that the upper part of the left ventral premotor cortex, an extension of this basic sensory-motor network, is apparently necessary for the uniquely human ability to precisely enumerate large numbers (Kansaku et al., 2004b). While it might be expected that the neighboring area of the premotor cortex activated in the current study is solely involved in sequential movement preparations rather than the counting process itself, this explanation is unlikely for several reasons. In Experiment 1, activation during counting of successive sensory stimuli was observed in the premotor cortex. In Experiment 2, completely naive participants showed similar patterns of premotor area activation, even in the absence of movement preparation. These results suggest that these areas are involved in enumerating sensory stimuli independent of whether a motor response is given. In Experiment 3, we found that the premotor cortex activation for counting did not depend on the timing or rhythm of stimulus presentation. The area did not show significant activation for the modality detection task, and a region-of-interest comparison confirmed that the premotor cortex activation was significantly stronger for counting than for modality detection.

It is possible that participants used internal speech while counting, and that the lateral premotor cortex activated because of subjects' internal verbalization of number words. We also assessed the issue in Experiment 3, and showed that the premotor cortex was not activated during internal speech of the number words. In a former fMRI study of overt and silent speech, Huang et al. found activation in a premotor area, but their specific areas of activation differed from the activation pattern found here, in other parts of the same general areas. The premotor activation they found for silent speech was mainly more inferior than the activation in the current study (Huang et al., 2002). There still remains a possibility that the area is related to some linguistic aspects of human counting, but the results of Experiment 3 suggest that the lateral premotor cortex was not activated by subjects' internal verbalization of number words.

In human neuroimaging studies, Simon et al. (2002) reported extensive frontal activation for basic numerical tasks that appeared to encompass the premotor cortex as well. Also, a recent study that investigated human neural correlates of approximate numerosity showed activation in the right premotor cortex, in addition to more significant activation in the intraparietal sulcus (Piazza et al., 2004). While previous studies have not focused on the role of the human premotor cortex in numerical processing, these studies of human numerical ability by Simon et al. and Piazza et al. did report premotor activation. Recently, Schubotz and von Cramon (2003) applied serial prediction tasks to determine that the lateral premotor cortex may play some role in non-motor cognitive processing. They proposed that the premotor cortex has a role in predicting sensory sequences and planning sequential actions. It is reasonable that the sequential prediction and planning functions of the premotor cortex would be co-opted and recruited for the fundamental abilities of sensory and motor enumeration, although further investigation using counting tasks and their serial prediction tasks in the same subject group is necessary to clarify dissociable roles in the premotor cortices.

In this study, another area that showed similar activation pattern with the premotor cortex was the medial premotor cortex: presupplementary motor area. Penfield reported that direct electrical stimulation in the medial frontal cortex, that includes the presupplementary motor area, inhibited the human subject's ability to count abstractly (Penfield and Welch, 1951). fMRI in humans indicates that the left presupplementary motor area activation increases with tasks of increasing arithmetic complexity (Menon et al., 2000). Taken together, these results suggest that the presupplementary motor area may also have some role in counting small numbers.

Other brain regions and sensory motor counting

Brain regions other than premotor cortices that showed activation during counting of successive events were in the posterior temporal cortex and the thalamus. The posterior temporal cortex showed activation in all tasks in all Experiments, including regular-timing, irregular timing, and modality detection. Significant activation in the superior posterior temporal cortex was bilateral in a conjunction analysis of consistent sensory and motor activation; it was more significant and extensive on the right than the left hemisphere. Activation in this area was not specific to the counting task or to the rhythm of stimulus presentation. These results indicate that superior temporal cortex may be involved in the most basic attentional process of detecting stimuli from different modalities and movements from different effectors.

In addition to the cortical regions, the thalamus was also activated during counting across all sensory modalities and motor effectors. Conjunction analyses across sensory and motor counting conditions revealed significant bilateral activation of the thalamus. Ojemann (1974) reported the dramatic effects of electrically stimulating the thalamus of a human subject while counting aloud abstractly. In Ojemann's study, stimulation of the left ventrolateral thalamus accelerated the rate of counting, stimulation of the right ventrolateral thalamus slowed the rate of counting, and both right and left stimulation caused an increase in counting errors. Although these results do not resolve the precise role of the thalamus for counting, they lend support to the significance of the thalamus in the counting network.

The area that showed obvious activation particularly in sensory counting was the posterior parietal cortex. The role of the intraparietal sulcus, which is a part of the posterior parietal cortex, in numerical abilities has been repeatedly documented and continually debated. While significant evidence supports the role of the intraparietal sulcus in symbolic numerical representations, two recent studies by Piazza et al. (2004) and Shuman and Kanwisher (2004) came to opposing conclusions as to whether the intraparietal sulcus also processes non-symbolic number information. In his analysis of these studies, Nieder (2004) concludes, based on Piazza et al.'s findings, that the intraparietal sulcus is likely to contain neurons responsive to number, and that the role of these neurons was not detected by Shuman and Kanwisher because they likely constitute a relatively small percentage of neurons in the intraparietal sulcus, most of which serve other functions. Neuroimaging studies by Lee and by Chochon et al. showed bilateral activation of this area during numerical subtraction. Lee (2000) proposed that this area is selectively involved in subtraction as opposed to multiplication, but Rickard et al. (2000) showed similar intraparietal activation in a multiplication verification tasks. Chochon (Chochon et al., 1999) reported a distinction in intraparietal lateralization based on numerical task, with left dominant activation for multiplication, bilateral activation for subtraction, and right dominant activation for magnitude comparison. Eger (Eger et al., 2003) found that the intraparietal cortex was selectively activated for visual or auditory numbers as opposed to letters and colors, and postulated a supramodal representation of number in the intraparietal cortex. The documented role of this area in subtraction, multiplication, comparison, and now small number enumeration tasks supports the possibility that this area contains a supramodal representation of numbers, but suggests that its functioning is more complex and may be hemispherically differentiated.

The observed areas that showed activation particularly in motor counting were the supplementary motor area, the left anterior parietal cortex, and the bilateral parietal operculum, irrespective of what body part was making the movement. Unlike the premotor and presupplementary motor area, which activated both for sensory and for motor counting, the supplementary motor area activated primarily during the sequential motor counting task. Given the supplementary motor area's well-documented role in planning, imagining, and preparing sequential movements (Tanji, 2001), it is likely that this area is more involved in preparing the sequential counted movement. In a monkey electrophysiology study, Sawamura et al. (2002) found number-selective neurons, which fired during sequential movements that consisted of 5 repetitive movements: push or turn, in the superior parietal lobule (part of area 5), an area corresponding to the anterior parietal activation seen here. A study by Nieder and Miller (2004) found that neurons in Area 5 do not respond to numerosity of visual displays. These findings support the results of the current study, which suggest that this anterior parietal area is particularly involved in enumerating movements, while the posterior parietal cortex is particularly involved in enumerating sensory stimuli.

The neural networks and the origin of number knowledge

The two previous neuroimaging studies that investigated human enumeration of small numbers have focused on the "subitizing" process for visual objects in a spatial array (Sathian et al., 1999; Piazza et al., 2002). In both studies, the visuo-spatial aspect of small number enumeration was investigated. The activated areas were mainly in the occipitoparietal areas, and the areas observed in the counting process were more widespread than in the subitizing process. Sathian et al. found posterior parietal activation for counting but not for subitizing. In contrast, Piazza et al. detected posterior parietal activation for both counting and subitizing. In this study, we also focused on the basic enumeration process for a small number of events, but particularly on enumerating successive events. We observed activation in the posterior parietal cortex during sensory counting but not motor counting. Also, we showed activations in additional areas, such as the lateral premotor cortex during sensory and motor counting, and the anterior parietal cortex specifically during motor counting.

To address the origin of number knowledge in the human brain, Simon focused on the convergence of theories of preattentional object representation: a theory of "object files" (Kahneman et al., 1992), in which object recognition occurs through abstract representational tokens, that initially carry no information about the object (details are filled in later), but are like place holders or files, that allow an infant or adult to keep track of multiple items in the world (Simon, 1997). Infants take advantage of this existing preattentional "object-file" mechanism for keeping track of objects in the world to determine one-to-one correspondences for numerical tasks up with sets of up to 4 objects, the apparent limit of this object file system. So Simon argues that infant basic numerical abilities are non-numerical in the sense that they take advantage of existing preattentional/attentional object processing machinery in the brain and co-opt it for taking on numerical tasks. Simon further argues that since this "object-file" system is based on a system of abstract representational tokens, place-holders for objects to keep track of that which precede any specific information of the object to be tracked, these object files are not necessarily limited to objects of a certain type or stimuli from any particular modality. Some behavioral studies also suggest a representation of number that is not modality specific (Jordan et al., 2005).

These theories also suggest that the abilities of humans, infants, and animals to enumerate up to 4 are based on the application of basic sensory-motor processing systems, capable of keeping track of sets of up to four items (Trick and Pylyshyn, 1994; Simon, 1997). The network activated by sensory and motor counting in this study appears to recruit more extensively areas already implicated in the most basic multimodal sensory-motor reaction paradigms (Kansaku et al., 2004a). A related set of studies indicates that the left upper part of the ventral premotor cortex, an adjacent extension of the premotor region activated in this basic sensory-motor network, is apparently necessary for the uniquely human ability to precisely enumerate large numbers (Kansaku et al., 2004b). The results of the current study reveal a network of areas involved in sensory counting across modalities and movement counting across effectors; this may provide support for Simon's hypothesis that an overlapping neural network enumerates small numerosities. The results also indicate that there may be some difference between the neural bases of motor counting and sensory counting, with these two processes recruiting distinct loci in the parietal cortex. Further studies of human adults, human infants, and monkeys could unravel the functional role of each of these areas and provide key insights into the origins of human numerical ability.

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