Attention modulates synchronized neuronal firing in primate somatosensory cortex

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A potentially powerful information processing strategy in the brain is to take advantage of the temporal structure of neuronal spike trains. An increase in synchrony within the neural representation of an object or location increases the efficacy of that neural representation at the next synaptic stage in the brain; thus, increasing synchrony is a candidate for the neural correlate of attentional selection[1]. We investigated the synchronous firing of pairs of neurons in the secondary somatosensory cortex (SII) of three monkeys trained to switch attention between a visual task and a tactile discrimination task. We found that most neuron pairs in SII cortex fired synchronously and, furthermore, that the degree of synchrony was affected by the monkey's attentional state. In the monkey performing the most difficult task, 35% of neuron pairs that fired synchronously changed their degree of synchrony when the monkey switched attention between the tactile and visual tasks. Synchrony increased in 80% and decreased in 20% of neuron pairs affected by attention.

Each monkey was trained to perform tactile and visual tasks and to switch between them when cued. The visual task was a dimming detection task: three white squares appeared on a computer screen and after a random interval one of the squares, selected at random, dimmed slightly. The tactile stimuli continued unabated during the visual task and were not coincident with the visual stimuli. Each monkey performed a different tactile task. Two monkeys discriminated raised letters (6.0 mm high) scanned across a distal fingerpad (15 mm s^{-1}), pressing a key when the letter on the finger matched the target letter displayed on a computer screen[2]. The height of the tactile letters was chosen to be close to the resolution limit in humans; the monkeys' performance was identical to that in humans discriminating the same letters[2]. The target letter displayed on the computer screen was large (>3° high) and stayed on continuously during the tactile task. For monkey M1, the target letter remained constant within trials in which a single set of neurons was studied (~45 min). For monkey M2, the target letter changed randomly after each correct response (every third or fourth letter on average; that is, about every 7.5–10 s). Monkey M3 discriminated whether bars (6.0 mm long) presented successively to a distal fingerpad had the same or different (by 90°) orientations. All three tactile tasks are difficult for humans, but M2's task is particularly taxing because of the continually changing tactile targets. The monkeys' responses were about 90% correct in all tasks. Each monkey was cued to switch between the tactile and visual tasks about every 7–8 min while simultaneous single-unit recordings were made from up to seven microelectrodes[3] located in the contralateral SII cortex an area known to be affected by attention[2,4,5].

Spike train data from each neuron pair were first sorted into blocks according to stimulus (particular letter or bar orientation) and task (tactile or visual). Two cross-correlograms were computed for each block—a raw correlogram between simultaneously

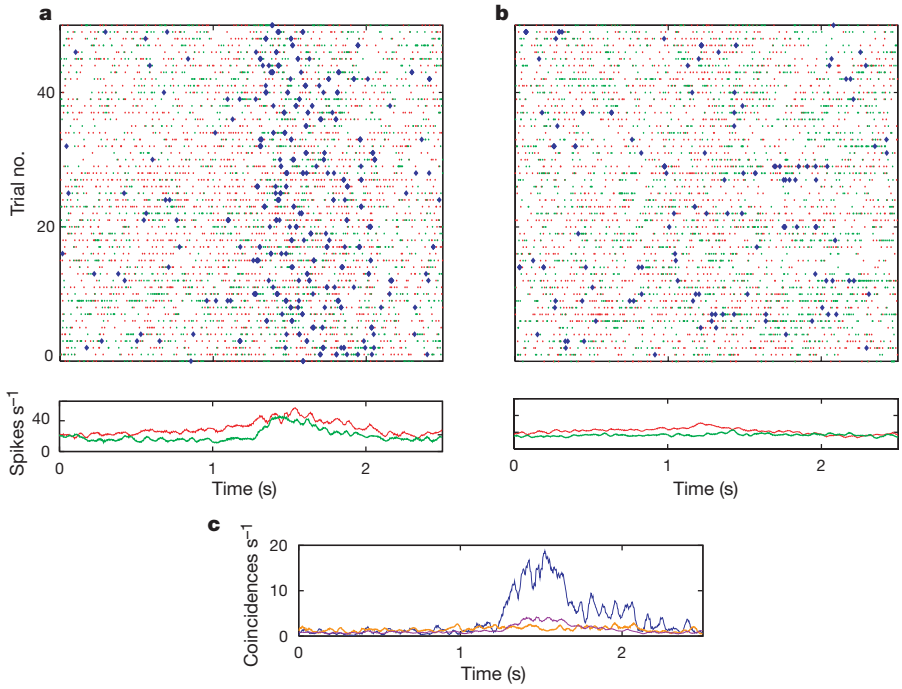

Figure 1 Responses of a typical neuron pair in monkey M2. Responses are triggered, at the onsets of 50 tactile stimulus periods, while the monkey is performing the tactile task (**a**) and the visual task (**b**). Each row in the raster represents one stimulus period, 2.5 s long, corresponding to the presentation of one letter. The letter enters the receptive field at about time (t) = 1.25 s. Red and green dots represent the action potentials of the neuron pair. Peristimulus time histograms (smoothed with a gaussian filter, s.d. 10 ms) are shown below each raster plot with corresponding colours. Synchronous events, defined as spikes from each neuron within 2.5 ms of each other, are represented as blue diamonds. The number of synchronous events is much higher when attention is directed towards the tactile stimuli. This change in synchrony is also apparent in the smoothed plots of rates of synchronous events shown in **c**; blue curve: tactile task; orange curve: visual task; violet curve: rate of synchrony expected by chance in tactile task. Note that all synchronous events are shown here whereas the statistical analyses subtract the estimated profiles of chance synchronous events.

recorded pairs of responses and a 'shift-predictor' correlogram between all nonsimultaneous pairs, which estimates the synchrony expected by chance. The shift-predictor corrected cross-correlogram (SCCC), which measures synchrony above or below that expected by chance, was computed by subtracting the shift-predictor correlogram from the raw correlogram. Synchrony was analysed in a 50-ms window (±25 ms around zero delay). Fifty milliseconds was chosen because about 70% of the neuron pairs with significant correlation peaks had half widths less than 50 ms, and 50 ms is approximately the period of perceptual integration for tactile stimuli[6].

Changes in synchrony between the visual and tactile tasks were assessed by computing the sum of squared differences between the bins of the visual and tactile SCCC's. We analysed only neuron pairs in which the spikes were collected on separate electrodes (400 μm minimal spacing) to ensure that the neurons were distinct. Spikes were determined visually to be well isolated from background noise and other spikes in all cases. The mean distance between recording sites exceeded 1,000 μm.

We analysed 648 pairs of responses from 436 neurons in SII cortex in four hemispheres of three monkeys. Seventy-eight per cent (339/436) of these neurons showed a significant change in firing rate when the animal switched between the tactile and visual tasks[2]. Sixty-six per cent (427/648) of the neuron pairs had significant cross-correlogram peaks ($P < 0.05$) during the visual task, the tactile task or both (Table 1). The high percentage of neuron pairs with correlated firing may be accounted for by the large, overlapping receptive fields in SII cortex.

Seventeen per cent (74/427) of the neuron pairs with significant cross-correlogram peaks also showed significant changes in synchrony between the visual and tactile tasks. Eighty per cent (59/74) responded with increased and 20% responded with decreased synchrony when the monkey performed the tactile task. Statistically significant synchrony was observed during both the visual and tactile tasks in most of these pairs. Figure 1 shows raster plots for a neuron pair in SII cortex of monkey M2 in which attention to the tactile stimulus produced a significant increase in synchrony. Synchronous events (spikes from two neurons within 2.5 ms of each other) are represented as large blue diamonds. The rate of synchronous events (Fig. 1c) rises to almost 20 s^{-1} as the stimulus letter passes over the fingerpad in the tactile task. During the visual task, the rate rarely exceeds 2 s^{-1}. A certain rise in synchrony is expected because the impulse rates in both neurons rise during the tactile task (Fig. 1a) but the rate of synchronous events expected by chance never rises above 4 s^{-1} (Fig. 1c, violet curve).

Representative SCCCs from each of the three monkeys are shown in Fig. 2. Figure 2a and b illustrates pairs with relative small and moderate increases in synchrony, respectively, when the animal switched to the tactile task. Figure 2c illustrates a neuron pair in which synchrony decreased. The abscissa on each inset histogram represents the mean change in the coincidence rate over the entire trial duration, the change in coincidence rate during the response is much larger than the mean value displayed on the abscissa.

The fractions of all neuron pairs with significant synchrony that also had significant changes in synchrony ($P < 0.05$) between the tactile and visual tasks (Table 1) were 16.0, 35.3 and 9.5% for M1, M2 and M3, respectively. When the criterion for significance was set at $P < 0.01$ the respective values were 8.6, 28.0 and 6.6%. When stated in terms of neurons rather than pairs the percentages were larger: of all the neurons involved in synchronous firing, 18.5, 53 and 26% in M1, M2 and M3, respectively were involved in one or more pairings in which synchrony changed significantly ($P < 0.05$). The probability of obtaining any of these percentages by chance is 0.003 in the worst case (M1 tested at $P < 0.05$; that is, the probability of obtaining 8 (16%) or more significant results in 50 cases when chance alone yields 2.5 cases (5%) is 0.003).

It is not surprising that only a fraction of the neurons in the population show significant changes in synchrony if change in synchrony is an important attentional mechanism. Neurons play different roles in perceptual processing. If only a subset of the neurons in a region are engaged in representing the attended stimulus, then only that subset should show increased synchrony. It is also not surprising that the fraction of neurons showing changes in synchrony is larger than the fraction of pairs; for example, if 30% of neurons belong to a particular subset then only 9% of all possible pairs draw both members from that subset.

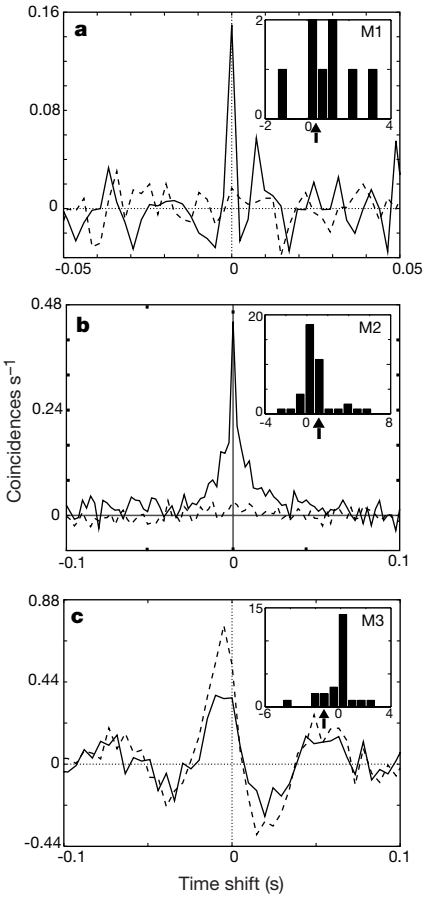

Figure 2 Shift predictor corrected cross-correlograms (SCCCs). Plots are for three pairs of neurons from monkeys M1 (**a**), M2 (**b**) and M3 (**c**). SCCC for the tactile and visual tasks are represented by the solid and dashed lines, respectively. The ordinate of each SCCC displayed here has been normalized to coincidences per second to account for differences in trial duration by dividing the counts in each SCCC bin by trial duration. The sum of differences between normalized tactile and visual SCCC bins (over ±25 ms) yields an overall measure of the change in rate of synchronous events. Insets show histograms of this overall change in rate of synchrony (coincidences s^{-1}) for all pairs with a significant attentional effect (see Table 1). Negative numbers in the histogram correspond to decreased synchrony in the tactile task. The arrow below each histogram identifies the change in rate of synchronous firing for the SCCC pair shown.

Table 1 Degree of synchrony in SII cortex

Monkey*	Synchrony†	Change‡	Increase§
M1	50/95 (52.6%)	8/50 (16.0%)	7/8 (87.5%)
M2	113/145 (77.9%)	41/116 (35.3%)	35/41 (85.4%)
M3	264/408 (64.7%)	25/264 (9.5%)	17/25 (68.0%)
Average	427/648 (65.9%)	74/427 (17.3%)	59/74 (79.7%)

*M1: letter discrimination, constant target; M2: letter discrimination, varied target; M3: bar orientation discrimination.
† Fraction of cell pairs with significant synchronous firing ($P < 0.05$).
‡ Fraction of neuron pairs in column two in which the synchrony changed between the visual and tactile tasks ($P < 0.05$).
§ Percentage of neuron pairs in column three in which synchrony increased during the tactile task.

The differences in numbers of affected neuron pairs between monkeys may have more than one explanation. One possibility is that the number of neurons engaged in representing statically indented bars is smaller than the number engaged by scanned complex forms such as letters; however, this does not explain the substantial difference between M1 and M2, both of which performed letter discrimination tasks. A second possibility, which may explain the difference between M1 and M2, is that the attentional demands differed between tasks. Human reaction times and error rates in a discrimination task are lower when the same reference pattern is presented repeatedly than when the reference pattern changes on every trial[7,8]. This is the principal difference between the tasks performed by M1 and M2. There is extensive evidence that the cognitive loads in the two experimental designs are different and that the second design is more taxing[7,8]. This difference in cognitive load may account for the larger percentage of neurons affected by attention in M2.

The temporal structure of spike trains has been suggested previously as a basis for information processing in the brain[9,10] and there are numerous reports of synchronous firing in the primate central nervous system[11–20]. Here, we investigated whether the degree of synchrony is modifiable and whether it changes when the animal changes its attentional focus. The changes in synchrony cannot be explained by stimulus-driven events as the tactile stimulus was identical in the visual and tactile tasks; nor can it be explained by attention-induced modulation of the neuronal firing rates, because we controlled for this effect with a shift predictor. The latter point was confirmed by an analysis showing that changes in the rate of synchrony were uncorrelated with changes in firing rate (measured as the change in summed rate; correlation, −0.0243). A lack of correlation between impulse rate and synchrony has been reported in a different context[14–16].

The changes in synchrony reported here are consistent with those predicted by theoretical analyses[21] and a computational model of attention[1]. That model, which motivated our study, accounts for the selectivity inherent in attention by a mechanism that increases synchrony in the representation of the location being attended in order to increase its synaptic efficacy. Whether that model is correct or not, increasing (decreasing) synchrony between neurons is a powerful mechanism for increasing (decreasing) the combined synaptic effect of a subset of neurons. If a significant number of the neurons that cooperate in the distributed representation of an object or location in space fire more (less) synchronously than neurons representing other objects or locations, then their combined message is more (less) potent. Change in synchrony may be an essential neural mechanism of selective attention. □

Methods

Animals and animal training

All surgical and experimental procedures were approved by the Animal Care and Use Committee of the Johns Hopkins University. Monkeys (male, rhesus, 3–5 kg) were placed on a restricted water diet and brought into the laboratory on 6 days a week for 4–5 months for training. They twisted a manual switch (M1) with their ipsilateral hand or pushed and pulled a foot switch (M2 and M3) to signal their responses and receive liquid rewards.

Recordings

Neural activity was recorded using seven separate extracellular microelectrodes driven by a Reitboeck microdrive[3]. The end of the microdrive was modified so that the seven electrodes were linearly aligned and spaced 400 or 600 μm apart. Electrode tracks were marked with dyes and standard histological techniques were used to confirm the recording sites in SII cortex[22]. Individual spikes were isolated using both a window amplitude discriminator and a template-based discriminator (Alpha Omega Corp). Only spikes that were determined visually to be well isolated and stable over the entire recording session were included in the analysis.

Data analysis

Blocks of tactile trials (animal performing the tactile task) were alternated with blocks of visual trials. Trial duration was 2.5 s (for M1 and M2) or 4.5 s (M3) and each analysis was based on at least four alternations between blocks[2]. A trial consisted of the presentation of one letter in the letter-discrimination task or a pair of bars in the bar-orientation task. Only tactile trials with correct responses were included in the analyses. Excitability covariation generated by long-term changes in rate[23] is unlikely (average correlation between paired rates was 0.055). Each trial was divided into 1,024 bins which yielded bin widths of 2.4 ms (M1 and M2) or 4.4 ms (M3). Raw cross-correlograms between pairs of neuronal responses were computed for individual trials and then averaged across all trials with the same stimulus (a specific letter or specific member of an orientation pair) and task (tactile or visual); this constituted an analysis block. The correlogram expected by chance was constructed by computing individual cross-correlograms between the responses of one neuron of the pair in each trial and the responses of the other neuron in every non-corresponding trial in the same analysis block and then averaging those correlograms. This average chance correlogram (the shift predictor) was subtracted from the average raw correlogram to obtain an estimate of the synchrony above or below that expected by chance. The final averaged shift-predictor corrected cross-correlogram (SCCC) for each task was then computed by averaging over all corrected correlograms.

The sum of squared SCCC bin values was used as the summary measure of synchrony. The sum of the squared differences, on a bin-by-bin basis, between SCCCs for the tactile and visual tasks was used as the measure of change in synchrony. Similar results were obtained with other test statistics (for example, sums and differences of absolute values). The first question addressed was whether individual SCCCs were different from those expected from chance synchrony between independent responses. This null hypothesis was tested with the Fisher permutation test[24]. The original data set was replicated exactly except that the response of one neuron in each trial was paired with a response of the other neuron, selected randomly and without replacement from another trial with the same stimulus and task. Then the analysis was repeated exactly as with the original data. Five hundred such replications produced the distribution of synchrony values that would have arisen if the neurons fired independently[25]. The second question was whether synchrony differed significantly between the tactile task and the visual task (the baseline condition). The null hypothesis is different from that in the first question above; it is that tactile and visual SCCCs may both display statistically significant synchrony but that they differ from one another by no more than a pair of visual SCCCs drawn at random. Random samples of the visual SCCCs were constructed by a bootstrap procedure[24], individual visual SCCCs were constructed by averaging single-trial cross-correlograms drawn randomly with replacement from the visual single-trial correlograms. Differences that would occur by chance under the null hypothesis were computed as the sum of squared differences between pairs of these visual SCCCs. The significance of the observed difference between the SCCCs derived from the tactile and visual tasks was computed as the fraction of differences resulting from the null hypothesis that exceeded the observed difference. Virtually identical results were obtained with bootstrap tests based on tactile SCCCs and a bootstrap version of the *t*-test. The use of these bootstrap procedures provides a model-free test of the degree of synchrony and does not assume any stochastic model of neural firing (for example, Poisson) or independence of firing in neighbouring time analysis bins[25].

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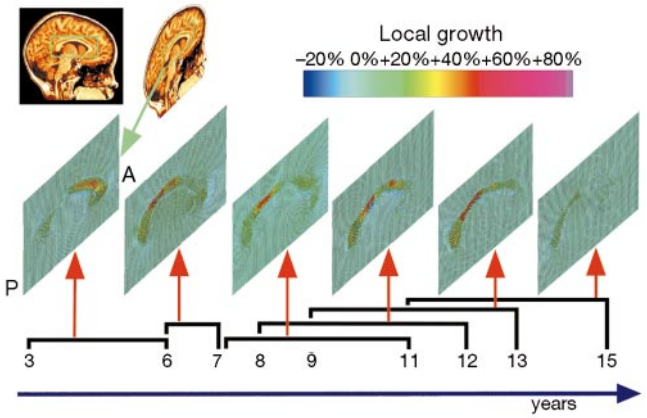

Figure 1 Growth patterns in the developing human brain detected at ages 3–15 years. A rostro-caudal wave of peak growth rates is detected in young normal subjects scanned repeatedly across time spans of up to four years. Between ages 3 and 6 years, peak growth rates (red colours; 60–80% locally) were detected in the frontal circuits of the corpus callosum, which sustain mental vigilance and regulate the planning of new actions. Older children displayed fastest growth at the callosal isthmus, which innervates temporo-parietal systems supporting spatial association and language function. Between ages 11–15 years, growth rates still peak at the isthmus, but are attenuated.

Growth patterns in the developing brain detected by using continuum mechanical tensor maps

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The dynamic nature of growth and degenerative disease processes requires the design of sensitive strategies to detect, track and quantify structural change in the brain in its full spatial and temporal complexity[1]. Although volumes of brain substructures are known to change during development[2], detailed maps of these dynamic growth processes have been unavailable. Here we report the creation of spatially complex, four-dimensional quantitative maps of growth patterns in the developing human brain, detected using a tensor mapping strategy with greater spatial detail and sensitivity than previously obtainable. By repeatedly scanning children (aged 3–15 years) across time spans of up to four years, a rostro-caudal wave of growth was detected at the corpus callosum, a fibre system that relays information between brain hemispheres. Peak growth rates, in fibres innervating association and language cortices, were attenuated after puberty, and contrasted sharply with a severe, spatially localized loss of subcortical grey matter. Conversely, at ages 3–6 years, the fastest growth rates occurred in frontal networks that regulate the planning of new actions. Local rates, profiles, and principal directions of growth were visualized in each individual child.

Time series of high-resolution three-dimensional magnetic resonance imaging (MRI) scans were acquired across large time spans from young normal subjects (aged 3–6, 6–7, 7–11, 8–12, 9–13 and 11–15 years) at intervals ranging from two weeks to four years. Growth patterns were recovered by computing a three-dimensional elastic deformation field, which reconfigures the anatomy at the earlier time point into the shape of the anatomy of the later scan.

Maps of local growth rates (Figs 1–4) revealed the complexity and regional heterogeneity of the tissue growth, pruning and maturation processes of late brain development. In subjects aged 6–15 years, the

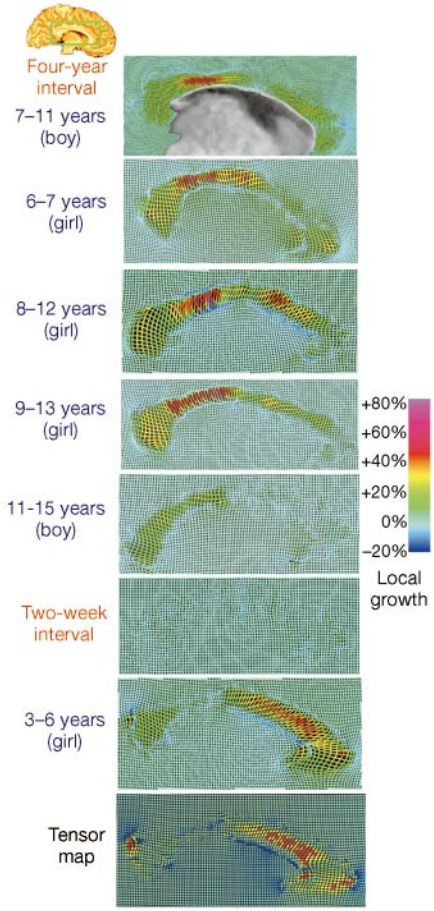

Figure 2 Mapping dynamic patterns of brain development: four-dimensional growth maps. Strikingly similar growth rates were detected in the corpus callosum of five young normal subjects scanned repeatedly aged 6–13 years. Peak values throughout the posterior midbody (red colours) were attenuated after puberty (11–15 years). By contrast, near-zero maps of change were observed between scans acquired over a two-week interval. Between ages 3–6 years, extreme growth rates were found in the anterior interhemispheric fibre systems that transfer information to sustain mental vigilance and organize new actions. Tensor maps identify the principal directions of growth rates, revealing an outward radial tissue expansion in frontal regions.