

Timing of human cortical functions during cognition: role of MEG

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Understanding of sensory and cognitive brain processes requires information about activation timing within and between different brain sites. Such data can be obtained by magnetoencephalography (MEG) that tracks cortical activation sequences with a millisecond temporal accuracy. MEG is gaining a well-established role in human neuroscience, complementing with its excellent temporal resolution the spatially more focused brain imaging methods. As examples of MEG's role in cognitive neuroscience, we discuss time windows related to cortical processing of sensory and multisensory stimuli, effects of the subject's own voice on the activity of their auditory cortex, timing of brain activation in reading, and cortical dynamics of the human mirror-neuron system activated when the subject views another person's movements.

The brain is a real-time processor and its functions can therefore be best studied with tools that allow tracking of neural activation with the millisecond time scale relevant for cortical dynamics during perceiving, speaking and moving. Only electroencephalography (EEG) and magnetoencephalography (MEG) can provide non-invasive information at such a high temporal resolution.

Compared with EEG, MEG has some advantages in identifying brain currents giving rise to the signals (see Boxes 1 and 2). The MEG signals are detected non-invasively outside the head with SQUID (Superconducting QUantum Interference Device) sensors. To determine the current distribution within the head, the magnetic field must be sampled at several locations, preferably simultaneously to avoid changes in the subject's state between the measurements. The modern neuromagnetometers consist of helmet-shaped multisensor arrays that allow the whole brain's magnetic field pattern to be recorded at once with even more than 300 SQUID sensors.

The MEG signals, arising from synchronous activation of neuronal populations, are usually in the femtoTesla (10^{-15} Tesla) range and thus only a tiny part of the steady magnetic field of the earth ($\sim 0.5 \times 10^{-4}$ Tesla) that just turns the compass needle. To avoid contamination by external artifacts, arising from moving metallic objects (such as cars and elevators) or from electric instruments and power lines, the recordings are typically carried out within a magnetically shielded room where all moving magnetic materials must be avoided. By using 'near-sighted' sensors, the recordings can be made less sensitive to distant noise sources as well as to biological artifacts arising from currents in the heart, muscles and eyes.

MEG can be used for detecting evoked and ongoing brain activity, both useful tools in studies of human cognitive functions. The evoked responses, elicited by various abrupt sensory stimuli, can be extracted from the background activity by means of time-locked averaging¹. The spontaneous activity contains distinct rhythmic components that in awake adults typically peak around 10, 20 and 40 Hz and react to various stimuli and tasks². Such rapidly changing phenomena can be studied only by EEG/MEG and not by blood-flow-related imaging methods such as PET and fMRI.

The MEG field patterns, recorded outside the head, are interpreted in terms of current distributions in the brain (Box 1). A surprisingly small proportion of cells can determine the measured signal: for example, 1% of synchronous pyramidal cells in a cortical area of 1 cm² could be responsible for 97% of the total signal³. The importance of synchrony for MEG (and EEG) signals, but not for fMRI or PET, accounts for some differences between the sensitivities of these methods. Changes in synchrony of the spontaneous firing, as well as changes in time- and phase-locking of the signals with respect to external events, or, for example, muscular activity⁴, are seen with MEG and EEG but not necessarily with fMRI or PET. On the other hand, MEG/EEG can be blind to the slowly rising or sustained neuronal activity that is associated with metabolic changes (see Box 2).

Time courses of evoked responses

When the generation sites of evoked responses are known (e.g. in the upper surface of the temporal lobe for the auditory evoked responses), the responses can be used as tools to study functions of these brain areas at a millisecond time scale. Recording responses to identical stimuli during different

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Box 1. The inverse problem and the sources of MEG signals

The inverse problem, that is, the deduction of neuronal currents from the measured external electric potential or magnetic field distribution, does not have a unique solution (Refs a,b). However, some solutions are more likely than others. By imposing constraints from anatomy, physiology, and other data, it is possible to limit the number of possible solutions to much fewer, and to form reasonable estimates of the source configurations. Encouraging agreement of such solutions has been obtained with data from other imaging experiments (Ref. c), lesions studies, and from intracranial recordings where the source sites and signal waveforms have been verified.

MEG and EEG reflect two sides of the same neuronal activation patterns, and the methods provide complementary information that is required to determine the brain's current distributions as accurately as possible. When the source pattern has been first found by MEG, for example, it is possible to use EEG as a cheaper method in several applications. It is also possible to design tailored electrode arrays on the basis of the MEG (or fMRI) findings for EEG monitoring of specific source sites.

The generators of MEG signals are typically modeled with one or several current dipoles. Although real dipoles do not exist in the brain, except at a very microscopic scale, the details of the current configuration in the source area cannot be detected at the typical measurement distance some 3 cm from the source, and thus the pattern produced by a cortical area smaller than 2 cm in diameter seems identical to a pattern produced by a real point-like dipole. Therefore a current dipole is a good model for local activation areas.

Identification of a single local source is straightforward, provided that the source current has a tangential component (and thus produces an MEG signal). However, when the source area is extended or when several areas are active at the same time, the field patterns may be very complex. One can then identify the first source at a time when the field pattern reliably suggests a single source or several sources far apart. For example, the primary somatosensory cortex SI can be identified at an earlier time after a tactile stimulus than the second somatosensory cortex SII (Ref. d); here the different current orientations markedly help the source differentiation. When necessary, the effects of known sources can be removed before identifying a new source (Ref. e). The complete model consists of several dipoles with time-varying strengths. An important final step is to compare waveforms predicted by the model with the measured signals.

A safe approach is to build up a complex model step-by-step, starting from known sources (e.g. those in sensory projection areas) and then adding more sources when needed (Refs f,g). Sometimes one also needs to use known anatomico-physiological constraints. For example, early tibial-nerve responses could be adequately explained either by one rotating, or two orthogonal, fixed dipoles (Ref. h). However, because no currents in the brain are known to rotate, the two-dipole model, although it contains more parameters than the one-dipole model, should be preferred. It is also possible to use constraints from other imaging modalities (PET, fMRI/MRI). For example, one might require that the currents obtained from the MEG solution are constrained to the cortical mantle, or one might use activation sites observed in fMRI/PET as seeds for the MEG analysis where the main task will then be to find the time course of activation (Ref. i). The fMRI-constrained MEG solution assumes that MEG sees all or a part of the same sources as those detected by fMRI. However, because of the synchrony issues, mentioned in the main text, this need not be the case. Naturally, if the fMRI-based constraints are not precise (for example, if the main fMRI activation is along a vein rather than in brain tissue), the fMRI-guided MEG solution will go wrong as well. The recently developed event-related fMRI paradigms allow rather similar experimental set-ups to be used both in electrophysiological and fMRI studies; even so, the time resolution of fMRI is limited by the relative slowness of the haemodynamic changes.

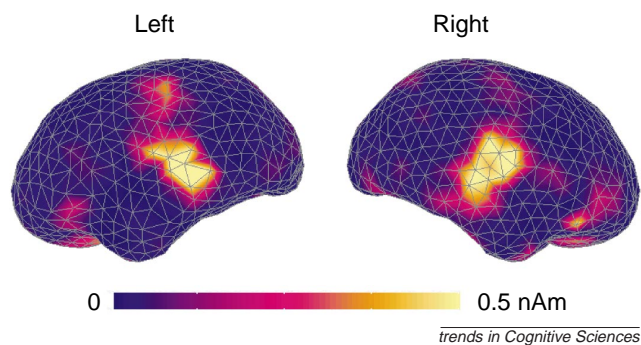


Fig. 1. Minimum current estimate (MCE) of brain activation. The MCE requires no explicit *a priori* information or any specific assumptions about the source configuration, and presents current distributions where the total sum of the current is as small as possible. Shown are the MCEs in the two hemispheres 80–130 ms after letters were presented auditorily.

It is also possible to use extended source models, for example, minimum current estimates (MCEs) that require no explicit *a priori* information or any specific assumptions about the source configuration (Ref. j) (Fig. 1). MCE presents current distributions where the total sum of the current is as small as possible, but it still explains almost all of the measured signals. The MCEs, transformed to a standard brain, can be averaged more reliably across subjects than the original signals or current dipoles.

One has to remember that the analysis result, a point-like or an extended source, largely depends on the analysis tools used. For example, a real point source will appear as an extended activation when analysed with a minimum-norm method whereas an extended source will appear point-like when analysed with a current-dipole model.

One way to test hypotheses of brain activation is to insert sources into certain regions of interest, determined on the basis of the particular subject's brain anatomy, then to calculate forwards the field patterns that would be produced by such sources, and finally to compare the predicted results with the measured data. Such an approach has been used to study activation of deep brain structures (Ref. k).

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Box 2. MEG in the study of human brain functions

The advantages and disadvantages of using MEG to study human brain functions are listed below.

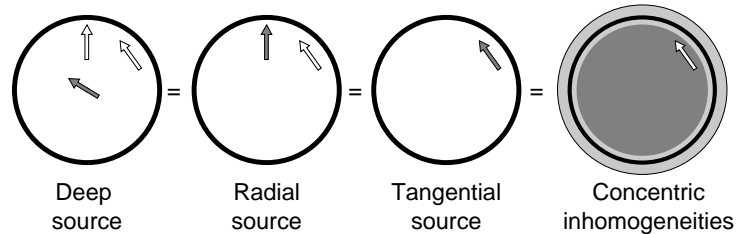
Advantages

- (1) MEG is totally non-invasive and can be repeated as often as desired in healthy subjects and patients.
- (2) MEG has excellent temporal resolution extending to the sub-millisecond range.
- (3) MEG reflects neural activation directly (mainly postsynaptic currents), rather than, for example, blood flow or metabolism.
- (4) Signals are typically evident without complicated statistical analysis (time-locked averaging is commonly used).
- (5) MEG is selective to activation of fissural cortex where currents flow tangentially to the skull; these areas are difficult to reach with other means, including intracranial recordings (see Fig. 1).
- (6) The tissues outside the brain (e.g. skull and scalp) do not significantly distort the magnetic field patterns generated by brain currents and recorded outside the head; this is an advantage over EEG (see Fig. 1).
- (7) MEG provides quantitative information about activation strengths of neuronal populations.
- (8) Conclusions can be made on the basis of single subject data, which allows studies of individual processing strategies. Therefore, group averages, which can be biased, are not necessary (although they can be useful in the initial analysis of a new data set).
- (9) Subtractions between conditions are not necessary, although they are possible – an important difference compared with PET and fMRI studies.

Disadvantages

- (1) The data interpretation is hampered by the non-uniqueness of the inverse problem (see Box 1). Therefore, MEG analysis typically relies on source modeling and is rather demanding for someone not familiar with the technique.

- (2) The neuromagnetometer has to be operated in a magnetically silent (often shielded) environment.
- (3) The subject has to cooperate and to keep the head immobile during the recording. This limits studies of some children, and recordings cannot be performed during major epileptic seizures.
- (4) The detected signals always reflect population responses (at least 1 mm² of cortex)
- (5) The most synchronous activation dominates the measured signals. This could of course be considered an advantage because the most synchronous activity might have a special role in the brain's signal processing.
- (6) Deep and radial sources are largely neglected (see Fig. 1). Identification of deep sources relies on forward calculations and on the use of information obtained with whole-head sensor arrays; such calculations are more accurate if a realistic volume-conductor model can be applied.
- (7) Activations of areas less than 2 cm apart can be difficult to discern if they do not differ in current orientation or timing.



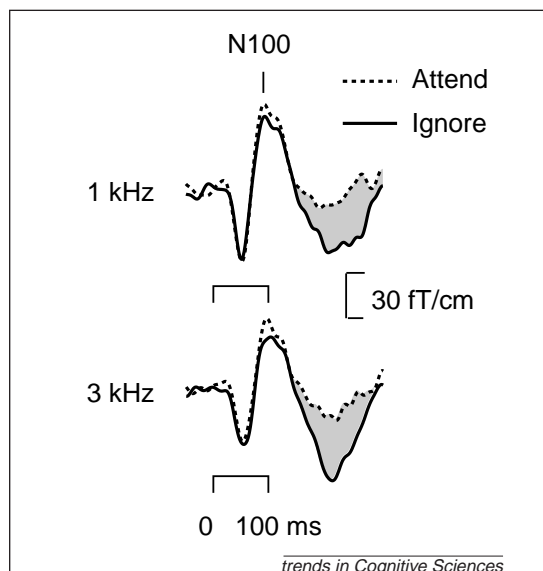
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Fig. 1. The properties of MEG in a nutshell. In all situations the external magnetic field is identical because in an ideal sphere, sources exactly in the middle of the sphere are always radial, radial sources anywhere in the sphere do not produce any external magnetic field, and because concentric inhomogeneities do not affect the magnetic field. EEG, by contrast, would pick up all these currents (tangential, radial, and deep) and be affected by the electric inhomogeneities.

mental states or tasks unravels temporospatial features of specific brain mechanisms.

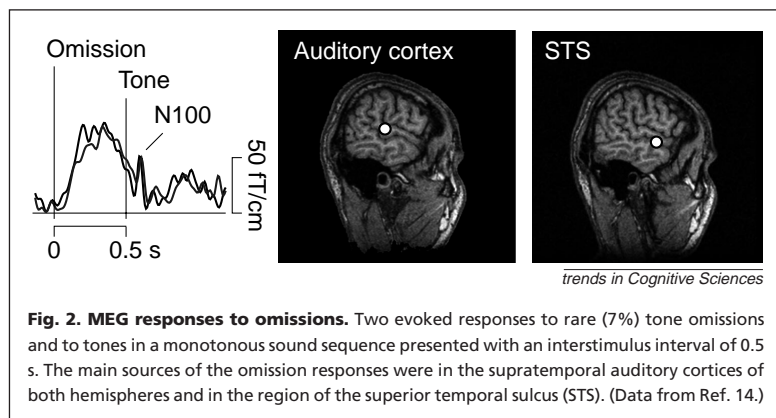
Although attention had been known to affect auditory evoked EEG potentials⁵, it was only the possibility of focusing with MEG on the functioning of the supratemporal auditory cortex that provided direct information about the role of the sensory-specific cortex during auditory attention. Figure 1 illustrates results from a study where the maximum attention effect occurred around 200 ms: low or high pitch tones were processed differently in the supratemporal auditory cortex when attention was directed to either of them in a monaural sequence⁶. Other MEG studies have shown that attention can modulate cortical activity already 20–40 ms after the sound onset, apparently reflecting early selection of input for further processing; modulation starts earlier when attention is directed to one ear during binaural stimulation than when one frequency channel is attended during monaural stimulation^{6–8}.

Evoked potentials typically decrease in amplitude when the interstimulus interval is shortened, with the strongest suppression effect in responses with the longest latencies. With the advent of MEG recordings, these recovery functions were interpreted in terms of lifetimes of memory traces left by the stimuli to different identified parts of the neuronal networks. The lifetimes of the memory traces were the shortest for the short-latency responses



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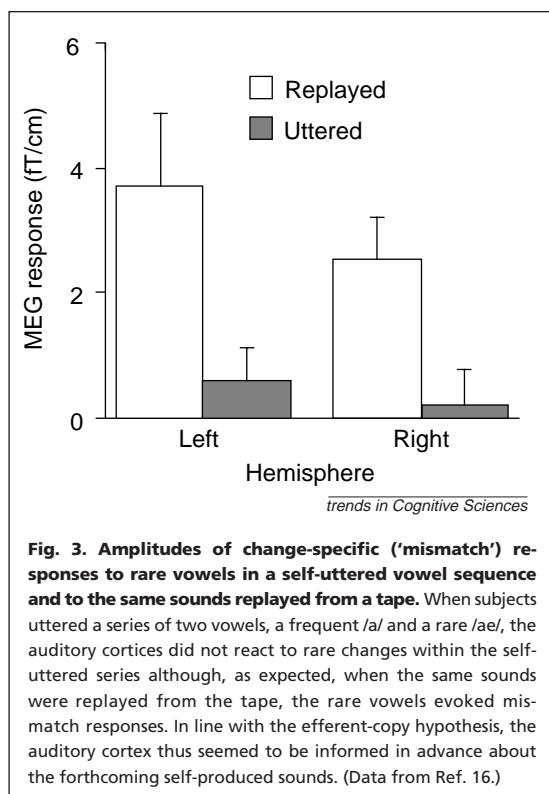
Fig. 1. Effect of attention on activity of the auditory cortex. The subject listened to a sequence of 1-kHz and 3-kHz tones and attended one of the two pitches in different runs (interstimulus interval = 405 ms). The differences between responses (shaded areas) indicate that identical tones are processed differently depending on the direction of attention. (Data from Ref. 6.)



generated at or close to the primary sensory projection cortices, and the longest ones for the long-latency responses, often originating outside the primary cortex. In the visual areas, for example, the traces typically decay within 0.2–15 s (Ref. 9): the shortest living traces occur at the primary visual cortex, the longest in the visual areas of the temporal lobe, and those in the motion-specific area V5 are in-between¹⁰. The long-latency auditory evoked responses, originating at the supratemporal auditory cortex, display trace lifetimes of up to 10–20 s (Ref. 11), and the traces seem to be of similar duration in both hemispheres¹². With MEG it is straightforward to follow activation of the auditory cortices separately in both hemispheres, whereas the corresponding EEG signals from the left and right auditory cortices sum up at the scalp midline and their separation requires source modeling¹³.

How the brain predicts the future

The nervous system is capable of predicting the future to some extent, and thereby of improving the organism's



adaptive behavior within its environment. The prediction performance can be studied in the human brain by first forming expectations and then leaving them unfulfilled, for example, by omitting a stimulus from an otherwise regular sound sequence. The subject, attending to such a sequence, has a peculiar feeling that the omissions are associated with temporally distinct percepts of 'nothingness' at about the time of the expected sound occurrence.

Figure 2 shows MEG data from such an omission experiment¹⁴. The sounds evoked, as expected, strong bilateral responses in the auditory cortex, with peak activity around 100 ms. Interestingly, the omissions were also associated with clear and broad MEG signals peaking at 150–200 ms, that is, some 50–100 ms later than the real sensory responses should have occurred. A considerable part of this response originated in the supratemporal auditory cortex, implying that the auditory cortex is not only involved in the analysis of incoming sensory signals, but that it also continuously compares the internal model of the world with the external environment. The omissions also evoked signals in the region of the superior temporal sulci (Fig. 2) and in the frontal lobes with right-hemisphere predominance. Although omission-related EEG responses have been known for a long time¹⁵, the MEG studies were the first to show where and when in the brain the sound-omission-related activations take place.

Listening to one's own voice

Hearing one's own voice forms an internal feedback system necessary for automatic monitoring of the pitch, intensity and phoneme quality of the speech. Curio *et al.*¹⁶ recently showed that self-uttered vowels activate the auditory cortex in a very similar phasic manner as external sounds do. However, in the left auditory cortex, the responses to self-uttered vowels were delayed on average by 11 ms compared with passive listening to the same sounds from tape. Thus the phonation affected the auditory function of the speech-dominant hemisphere, probably through a cortico-cortical feed-forward ('efferent copy') signaling from the motor centers to the auditory cortex. The finding is in line with monkey studies demonstrating a motor-to-sensory inhibitory influence during vocalization¹⁷.

As an outcome of the efferent copy, the auditory cortex should not be 'surprised' by infrequent changes in a self-uttered monotonous vowel sequence. The MEG results support this hypothesis¹⁶ (see Fig. 3): rare changes in self-uttered sounds did not elicit any extra response from the auditory cortex, but, as expected, in the replayed sequence the rare vowels elicited mismatch responses¹⁸. In line with the efferent-copy hypothesis, the auditory cortex thus seemed to be informed in advance about the forthcoming self-produced sounds. These findings reflect interactions between audition and phonation on a millisecond time scale.

Face-related activation

Recent fMRI data suggest that the fusiform face area (FFA) is strongly influenced by the subject's experience and learning, and that it has a rather general role in categorical visual perception^{19,20}. Halgren *et al.*²¹ studied the stimulus-

specificity of the FFA by exploiting the MEG's property to provide quantitative measures of activation strengths. Such measures are derived from MEG source analysis; fortunately they are not affected by the electric conductivity pattern of the head that smears the EEG distribution (see Box 2) nor by the depth of the source that affects the signal amplitudes. The face-specific responses peaked around 165 ms and were clearly stronger to photographs than to schematic sketches of faces, or to pictures in which the locations of facial features were scrambled. On the basis of the response latency, the authors considered FFA to be in the cortical processing sequence between the early retinotopic visual areas and the later multimodal cortices involved in cognitive integration (assumptions and possible pitfalls of this type of timing analysis are discussed in the Conclusions below).

Seeing speech and hearing touch

Our everyday sensory inputs are multimodal and their temporal coincidence helps the brain to construct an idea of a unique object or event. Multisensory integration typically has a rather broad time window^{22,23}. In movies, for example, time lags of the order of 100 ms between the sound and picture can go unnoticed. Similarly, audiotactile interaction tolerates delays of tens of milliseconds between auditory and tactile inputs²⁴.

In face-to-face communication, seeing the speaker's articulation movements strongly supports speech perception and even normally hearing subjects benefit from lip reading; thus visual input can improve the signal-to-noise ratio of auditory processing. Visual information about articulation can also change the auditory percept as happens during the McGurk illusion²⁵ when the subject observes videotaped articulation of some phonemes and at the same time hears different phonemes from the soundtrack. MEG recordings during the McGurk illusion have shown that the visual input from the mouth movements affects, after around 180 ms, the processing of the sounds by the auditory cortex or its neighbouring areas²⁶. A more recent fMRI study²⁷ supports this interpretation, showing activation of the auditory cortex during silent speechreading.

Levänen *et al.* studied a congenitally deaf subject whose auditory cortex did not respond to any sounds²⁸. Surprisingly, however, tactile stimulation of the palms and fingers evoked strong responses in the auditory cortex, and the responses even differentiated between vibration frequencies of 180 versus 250 Hz (Fig. 4). This finding was unexpected because anatomical pathways from skin to the auditory cortex had been unknown. However, recent intracranial recordings in monkeys have shown that somatosensory input reaches the auditory cortex²⁹. It is thus possible that when input from one sensory modality is deprived from an early age, the originally suppressed connections from other modalities become unmasked. Interestingly, the current direction during these MEG responses was the same as seen during the long-latency auditory evoked responses and mismatch fields³⁰, thereby further demonstrating that the vibratory stimuli activated the auditory cortex in a very 'normal' manner.

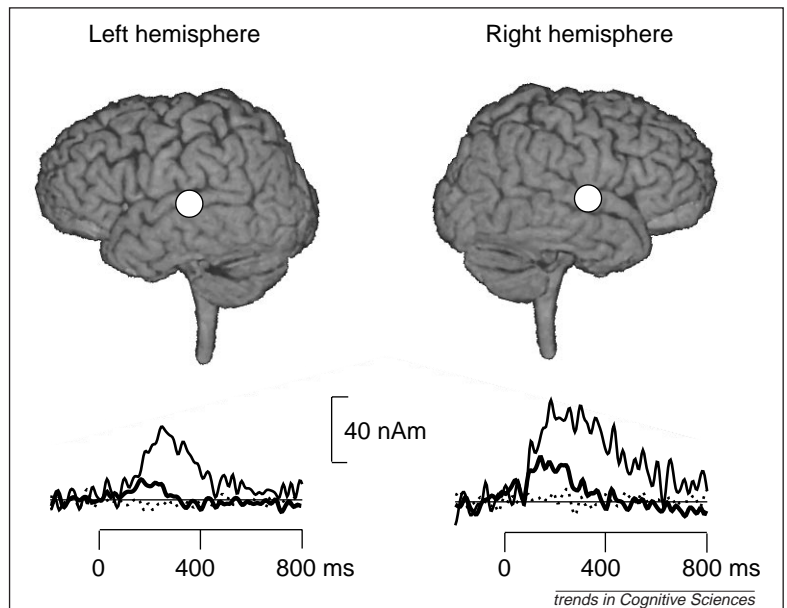


Fig. 4. MEG responses from the auditory cortex of a congenitally deaf subject. Activation of the auditory cortex (circles denoting the activated area projected from the depth of the Sylvian fissure to the surface of the brain on the MRI surface rendering) of a congenitally deaf subject with vibrotactile stimulation of the palms and fingers²⁸. The stimuli were presented in an odd-ball manner, 250-Hz bursts as standards and 180-Hz bursts as deviants. Thick traces, responses to standard stimuli; thin traces, responses to deviant stimuli. The dotted lines refer to the situation when the subject did not keep the hands on the tube; in that condition the auditory cortex did not react.

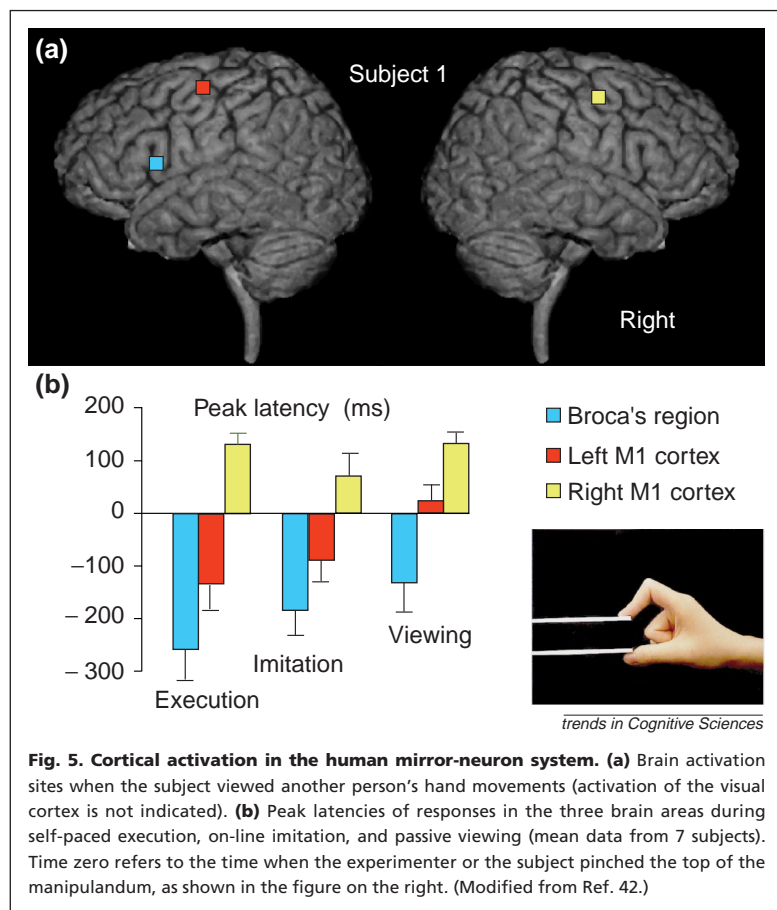
Audiovisual integration of letters

Some intermodal interactions are culture-related. For example, reading is based on learned associations between auditory and visual forms of letters. To investigate the neural representations of such audiovisual objects, Raij *et al.* recently recorded neuromagnetic cortical responses to auditorily, visually, and audiovisually presented single letters³¹. The most prominent intermodal interactions were seen in the right temporo-occipito-parietal junction at 280–345 ms and in the superior temporal sulci (STS) of both hemispheres at 380–540 ms. These multisensory brain areas apparently support the supramodal concept of a 'letter'. The STS regions are also activated, with a similar time course, during visual imagery of letters³², suggesting similar supramodal activations for perception and mental imagery. The observed activation of the STS region with audiovisual letters nicely agrees with a recent fMRI study that identified an integration area for audiovisual speech (articulation movements combined with speech sounds) in the left STS³³.

Timing in dyslexic readers

Reading is a complex skill, executed by brain mechanisms that certainly did not develop specifically for that purpose during evolution. It is thus not surprising that at least one in every 20 subjects confronts problems with fluent reading despite normal intelligence and proper education.

Helenius *et al.* presented to normal and dyslexic readers visual sentences, one word at a time³⁴. The beginning of each sentence created a high expectation for a certain final word. The brain areas involved in the semantic processing of the final word were generally similar in both groups, with consistent activity, for example, in the left superior



temporal cortex. However, the activation of this area was significantly delayed and weaker in dyslexics. The results were interpreted to reflect problems of dyslexics in pre-semantic analysis so that smaller or less synchronized neuronal populations were activated in their temporal cortex during reading comprehension. Whereas normal readers perceive a word as a whole, the reading of dyslexics appeared to advance in units of letters or syllables. A previous MEG study had implied that dyslexic subjects use guessing, reflected in prominent activation of the Broca's region, to compensate for difficulties in recognizing words³⁵.

Action viewing and the human mirror-neuron system

Humans copy other persons' actions during their whole life, effortlessly and unconsciously. Recent data suggest that this type of automatic imitation behavior is supported by a 'mirror-neuron system', first identified and characterized in the monkey brain.

Rizzolatti and co-workers³⁶ observed that the monkey premotor cortex contains 'mirror neurons' that discharge both when the monkey executes hand actions itself and when it observes the same action made by another monkey or the experimenter. This mirror-neuron system was assumed to match action observation and execution and thereby to play an important role both in action imitation and in understanding the meaning of actions made by other subjects. The mirror-neuron system could thus form an important link between a sender and receiver of a motor-act-based message.

The first indication of the existence of a corresponding action observation/execution matching system in the

human brain was obtained by PET³⁷ and transcranial magnetic stimulation³⁸ studies. A recent MEG study³⁹ was designed to find out whether the primary motor cortex would be involved in the human mirror-neuron system. The functional state of the motor cortex was probed by monitoring the level of the 20 Hz frequency component of the mu rhythm that increases transiently within 500 ms after electric median nerve stimuli. The early suggestion that this 'rebound' reflects active inhibition in the motor cortex⁴⁰ has been confirmed by a recent transcranial magnetic stimulation study that showed decreased motor cortex excitability after median nerve stimuli, with a time course corresponding to the rebound of the 20 Hz motor cortex rhythm⁴¹. This rebound was totally abolished when the subject manipulated a small object. Most interestingly, the rebound was also significantly diminished during action observation³⁹. The results thus demonstrated that the primary motor cortex is a part of the human mirror-neuron system.

In a more recent MEG study⁴², aimed at identifying the temporal dynamics of the cortical activation sequence within the human mirror-neuron system, subjects performed, observed or imitated right-hand reaching movements which ended with a precision pinch of the top of a manipulandum (Fig. 5). In all these conditions, the main activations were found in the left occipital visual cortex, the left posterior inferior frontal area (BA44; Broca's area) and the bilateral primary motor areas. All these areas are thus involved in the human mirror-neuron system.

Figure 5 shows the relative timing of the activated areas. During execution, the left BA44 was activated first (peak ~250 ms before the pinching), followed within 100–200 ms by activation in the left primary motor area (BA4), and 150–250 ms later in the right motor cortex. During imitation and observation, the relative timing of the Broca's and the motor cortex areas was similar as during action execution (Broca → left motor cortex → right motor cortex) whereas activation of the occipital cortex varied in different conditions, depending on at which phase of the motor sequence the hand (the visual stimulus) appeared in the subject's view. Both BA44 and motor cortex were activated about twice as strongly during on-line imitation than during self-paced execution and passive observation. Only the occipital activation was detected when the subject observed the experimenter's hand to reach the manipulandum without pinching.

These results strongly suggest that the Broca's region, the human counterpart of the monkey mirror-neuron area F5, acts as an orchestrator for the human mirror-neuron system. According to Rizzolatti and Arbib⁴³, the precursor of the Broca's area might have played a crucial role during evolution of interindividual communication by orofacial and hand gestures, and might even have formed the gestural basis for the evolution of speech production.

Subjects with autism are impaired in mindreading and imitation skills. Avikainen *et al.*⁴⁴ thus tested the possibility that the mirror-neuron system of subjects with Asperger syndrome (AS), a mild autistic disorder, would not function properly. All subjects failed in theory-of-mind tests that probed the subject's ability to understand other

persons' mental states⁴⁵. However, viewing hand actions modified the neuromagnetic ~20 Hz oscillatory activity in the primary motor cortex approximately to the same extent in both AS subjects and controls. Thus impaired mind-reading and imitation skills found in AS and autism do not seem to result from significant dysfunction of the motor-cortex part of the mirror-neuron system. Future studies should explore other parts of the mirror-neuron system in autistic subjects.

Conclusions

Accurate timing is essential for a multitude of brain functions. The relevant time windows differ greatly, extending from a fraction of a millisecond for directional hearing to tens of seconds for sensory and working memory. MEG is well suited for studies of fast activation sequences of human cortical functions, and it also allows comparison of timing between distinct brain regions. Small time differences, such as the roughly 20-ms delay from sensory receptors to the first cortical activation, can be monitored non-invasively only by electrophysiological methods.

How does the obtained timing information then contribute to our understanding of brain functions? Anatomical wiring diagrams are often used to define the hierarchical structure of signal processing in the brain. In a strictly serially connected neuronal network, activation onset times at different nodes give direct information about the hierarchical position of that node within the whole processing chain. However, the situation becomes immediately much more complicated when the network also contains feedback connections, through which signals can be modulated at an earlier processing stage or through which some nodes may display several activation 'waves'. In addition, different pathways may have considerably different conduction times (for example, the magno- and parvocellular visual pathways, or the tactile versus pain fibers in the somatosensory pathways), and thus the response onset or peak latencies do not necessarily agree with the hierarchical level of a certain processing stage. A further complication is that not only the conduction velocities, but also the pattern of convergence⁴⁶ and the mass action due to number of fibers may affect the relative timing. Moreover, bypass routes between the nodes of the hierarchically organized networks can drastically change the activation order.

Recent electrophysiological recordings in the monkey visual system^{47,48} indicate that the functional hierarchy, derived from the relative activation latencies of various visual areas, is not at all so clear as one might predict from the available anatomical information. For example, distributions of onset latencies of cortical firing overlap heavily in areas V1, V3, MT, and the frontal eye field⁴⁸. The functional significance of this overlap is at present totally unknown. To further develop models of the neural basis of cognitive functions, it is important to obtain more accurate and extensive information about the relative timings of activations at different parts of the brain, naturally combined with converging anatomical information. Given the considerable jitter in response latencies at different brain areas, one might speculate that the most synchronous activation,

Outstanding questions

- What is the role of timing in cognition and what are the important time windows for different brain functions? Sub-questions here include: How do we interpret the timing information in terms of serial versus parallel pathways, and in terms of hierarchical organization of cortical signal processing? What do onset and peak latencies tell about the activation sequence? What is the functional significance of the successive evoked response deflections? Do cortical activation sequences differ in subjects with special abilities?
- What important aspects of local neuronal processing are neglected by looking at MEG/EEG signals that mainly reflect net current along the cortical pyramidal cells, which are oriented parallel to each other?
- What are the limits of MEG technology? Can the spatial resolution be improved? Will development of high-temperature superconductors lead to totally new instrument designs? What kind of progress can be expected in data analysis?
- How can EEG and MEG be combined in a feasible way to detect both the tangential and radial currents? How can we determine accurately and easily the conductivity structure of the head, necessary for EEG source calculations? How can we determine the extent of the active brain area? How can MEG and fMRI information be combined without too much smearing in either the spatial or the temporal domain? Is there a 'golden standard' method to be used as the reference for brain activation patterns when several imaging modalities are combined?
- How can real-life-like experimental set-ups be developed, with natural stimuli and tasks, despite the constraints of MEG that the subject has to keep the head immobile during the recording and that all equipment must be non-magnetic?

readily observed by EEG/MEG, has some specific functional significance.

Each brain is different and the active areas differ between individuals in similar tasks. It is to be expected that the individual processing strategies are reflected even more clearly in the timing than in the sites of cortical activation. MEG studies can contribute to the understanding of cerebral activation sequences in healthy subjects and in patients with neurological or psychiatric diseases, as well as in persons with special cognitive abilities.

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