

Research article

Direction of magnetoencephalography sources associated with feedback and feedforward contributions in a visual object recognition task



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HIGHLIGHTS

- Fusiform sources in a visual object recognition MEG experiment were examined.
- Directions of source currents were opposite for expected feedforward and feedback inputs.
- MEG and EEG source direction may depend on hierarchical organization.

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ABSTRACT

Identifying inter-area communication in terms of the hierarchical organization of functional brain areas is of considerable interest in human neuroimaging. Previous studies have suggested that the direction of magneto- and electroencephalography (MEG, EEG) source currents depend on the layer-specific input patterns into a cortical area. We examined the direction in MEG source currents in a visual object recognition experiment in which there were specific expectations of activation in the fusiform region being driven by either feedforward or feedback inputs. The source for the early non-specific visual evoked response, presumably corresponding to feedforward driven activity, pointed outward, i.e., away from the white matter. In contrast, the source for the later, object-recognition related signals, expected to be driven by feedback inputs, pointed inward, toward the white matter. Associating specific features of the MEG/EEG source waveforms to feedforward and feedback inputs could provide unique information about the activation patterns within hierarchically organized cortical areas.

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1. Introduction

Non-invasive methods such as magneto- and electroencephalography (MEG, EEG), and functional magnetic resonance imaging (fMRI) provide means to examine neural activity in various ways, for example, by determining locations, sequences, and connectivity patterns among regions in the human brain [39]. In addition to these measures, identifying inter-area communication in terms of the hierarchical organization of functional brain areas

would be highly relevant in the quest for understanding the operation of the brain. Characteristic anatomical laminar distributions of input and output connections between cortical areas have been described as being of feedforward, feedback, or lateral type, thereby defining a hierarchical organization among the areas [15,36]. However, this type of information is not readily available in human imaging data. The spatial resolution of fMRI is approaching the level at which laminar distributions of cortical activity can be detected [35]. The direction of the MEG and EEG source currents is another piece of information that may help to characterize layer-specific input patterns into a cortical area, thereby providing cues about the flow and the function of the detected neural activity in terms of feedforward (bottom-up) and feedback (top-down) of inputs [18,23].

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MEG and EEG signals originate mainly from post-synaptic currents in cortical pyramidal cells [33], and the direction of the source current depends on the type and the dendritic location of the synaptic input [5,27]. In event-related response waveforms, an initial deflection can often be associated with feedforward input, followed by broader feedback-related activity [3]. In somatosensory, auditory, and visual evoked MEG data, early biphasic or triphasic responses, presumably driven by feedforward inputs, and later uniphasic feedback driven responses have been observed [18–20]. Given the different laminar distributions of feedforward and feedback type inputs, it is conceivable that the direction of the initial phase of a feedforward driven response is opposite to that of a feedback driven response. Biophysically realistic computational neural modeling incorporating detailed physiology of the laminar structure in cortical circuits has been successfully applied to interpret the directionality of neural current sources underlying MEG signals during a somatosensory detection task [22,23,41]. In the present study, we examined the direction in MEG source currents in the fusiform region in a visual object detection experiment in which there were specific expectations of activation being driven by either feedforward or feedback inputs [9].

2. Methods

The present results were derived from new analyses applied to previously published MEG data from a visual object recognition experiment [9]. In this experiment, the experimental evidence supported specific theoretical predictions regarding latency- and condition-dependent feedforward and feedback inputs to the inferior occipitotemporal (fusiform) region. According to the model of Bar [7,8] (Fig. 1A), low spatial frequency information about the visual object is quickly passed to the orbitofrontal cortex. Previously, activity associated with successful recognition of objects was found to occur earlier in the orbitofrontal cortex than in the fusiform region [9]. This is consistent with the orbitofrontal cortex enabling top-down facilitation of object recognition by sending predictions about the object identity to the fusiform cortex. Therefore, feedback-type input into the fusiform region is expected for those trials in which the subject recognized the object. The fusiform region is also expected to receive feedforward-type input through a bottom-up route along the ventral visual pathway. Thus, the fusiform region is expected to receive both top-down feedback-type input as well as bottom-up feedforward-type input. Here, we determined the direction of the MEG source current in these cases to evaluate whether the source direction is dependent on the input type.

Nine healthy volunteers (6 females, age range 22–30 years) performed a visual object recognition task during the MEG recordings. The protocols were approved by the Internal Review Board at Massachusetts General Hospital; written informed consent was obtained from all subjects. Line drawings of familiar objects were presented on a computer screen for 63 ms, preceded and followed by random-dot mask patterns for 27 ms and 108 ms, respectively. Subjects were instructed to recognize each of the objects and to indicate their level of knowledge about the identity of the object by pressing one of four response buttons. MEG signals were obtained using a 306 channel Vectorview system (Elekta Neuromag, Finland), comprising of 204 planar gradiometers and 102 magnetometers. The sampling frequency was 600 Hz with a 0.1–200 Hz band-pass filter. Responses were low-pass filtered off-line at 20 Hz. Epochs were baseline corrected by subtracting the mean of the 500 ms pre-stimulus interval in each sensor. For details of the experimental setup, see [9].

The direction of the source currents was examined using a distributed source model, the minimum-norm estimate (MNE) [17]. The MNE-based estimates of the time course of the source currents

in the left and right hemisphere fusiform gyrus regions-of-interest (ROIs) were obtained [9]. The MNE was computed by assuming that all sources were located on the cortical surface extracted from anatomical MR images; a loose orientation constraint and depth-weighting were applied [25]. To determine the direction of the source currents, the source components normal to the cortical surface was extracted. The MNEs were constructed for each individual subject; the waveforms were computed as the mean value of the amplitude of the discretized source elements within the ROIs. In addition to the MNE analysis, the location and the direction of the fusiform sources in individual subjects were illustrated with equivalent current dipoles.

For the practical estimation of the MEG and EEG source direction, it is helpful to make a distinction between the physiological direction and the physical orientation of the source current. MEG and EEG are highly sensitive to the physical orientation of the source [1], which usually can be reliably determined [29]. However, identifying the physiological direction of the source (i.e., outward vs. inward with respect to the white matter), accurate localization of the source with respect to the cortical anatomy is essential: if the source is mis-localized to the opposite bank of a sulcus, an erroneously reversed direction will be inferred. Here, the tangentially oriented fusiform source currents were mainly on gyral parts of the inferior surface of the occipitotemporal region [9]; thus, they were well suited for reliable determination of the physiological source direction using MEG.

Two specific cases of fusiform activation were examined. The first was non-specific early evoked activity, obtained from all recognized trials in the latency window 100–120 ms after the appearance of the first visual masking stimulus. This early activity is assumed to result from feedforward input to the fusiform region, presumably from the occipital visual cortices. The second case was the later, recognition-related activity, obtained from the difference between conditions (recognized minus unrecognized trials, 210–250 ms). This recognition-related would be consistent with resulting from feedback-type top-down facilitatory inputs from the orbitofrontal cortex, which showed activation around 130 ms in the previous study [9]. For statistical analysis, a *t*-test was performed for the MNE-amplitude of the left and right hemisphere fusiform ROIs for the two cases against the null hypothesis of the mean amplitude across the subjects being zero.

3. Results

Measured MEG field maps and the corresponding equivalent current dipoles for one subject are shown in Fig. 1B. The early visual evoked response at 110 ms suggested a source in the right inferior occipitotemporal cortex, pointing outward, i.e., away from the white matter. In contrast, the differential signals for recognized and not recognized trials at 260 ms suggested later bilateral inferior occipitotemporal sources pointing inward, toward the white matter.

Results from a distributed source analysis of the MEG data confirmed the reversal of the source direction between the two conditions. Source waveforms for the left and right fusiform ROIs, averaged over nine subjects, are shown in Fig. 1C. A *t*-test indicated significant positive (outward direction) source amplitude for the 100–120 ms latency window of the initial visual response (right hemisphere: $t_{df=9} = 4.01$, $p = 0.003$, uncorrected; left: $t_{df=9} = 5.26$, $p = 0.0005$), and negative (inward) amplitude for the 210–250 ms window of the recognition-specific subtraction data (right: $t_{df=9} = 2.58$, $p = 0.03$; left: $t_{df=9} = 4.21$, $p = 0.002$).

4. Discussion

The opposite directions of the estimated MEG source currents for the fusiform gyrus in the two experimental conditions are

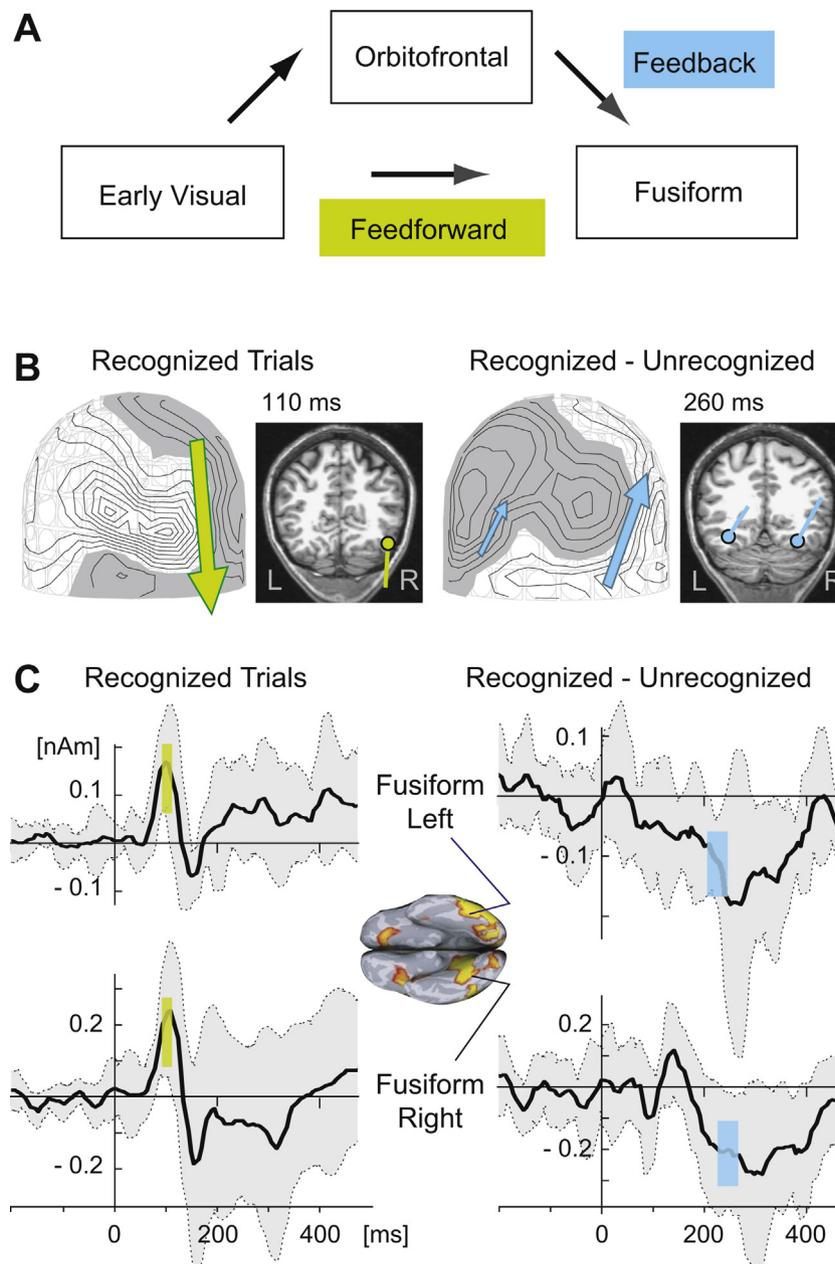


Fig. 1. Direction of MEG source currents in a visual object recognition experiment.

A. Sequence of cortical activation during visual object recognition, according to Bar et al. [9]. The fusiform area is expected to receive inputs from both higher and lower areas in the hierarchical organization: feedback-type input from the orbitofrontal cortex representing top-down facilitation and feedforward-type input from the early visual areas.

B. MEG data from a single subject, depicting visual evoked response at the latency of 110 ms, in data averaged over all trials in which the subject recognized the object (left), and differential object recognition specific response at 260 ms in subtraction data (recognized vs. un-recognized object trials; right). The isocontour maps (40 fT between lines) depict the normal component of the magnetic field over the back of the head. The arrows represent equivalent current dipoles fitted to the MEG. The dots indicate the dipole locations in the inferior occipitotemporal area on magnetic resonance images. Note that the direction of the dipoles reversed between these two cases in which feedforward and feedback inputs are expected: dipoles pointing outward/inward are shown in green and blue, respectively.

C. Estimated MEG source waveforms for inferior occipitotemporal (fusiform) regions-of-interest in the left (top) and right (bottom) hemispheres, obtained using a distributed source model. The shading indicates one standard deviation above and below the mean value across nine subjects. For the early visual evoked activity (left), positive amplitude, corresponding to outward polarity, was observed in both hemispheres at 100–120 ms (green bars). For the difference data, object recognition specific response (right) the estimated source had negative, inward direction at 210–250 ms (blue). These data are consistent with the source currents being of opposite direction for feedforward and feedback inputs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

consistent with a dependence between the source direction and the type of information flow within a hierarchically organized network of cortical areas. Feedforward inputs connect to the middle parts (granular layer 4), whereas feedback type inputs connect mainly superficially (supragranular layers 1–3) and also to some extent to the deep layers (Fig. 2A) [10,15,36]. Biophysical

computational modeling studies have suggested that excitatory input to granular layers (feedforward type input) subsequently propagating to supra- and infragranular layers can create outward directing current source, whereas input to supragranular layers (feedback) creates a source in the opposite, inward direction [22,23]. The present results are in accordance with this

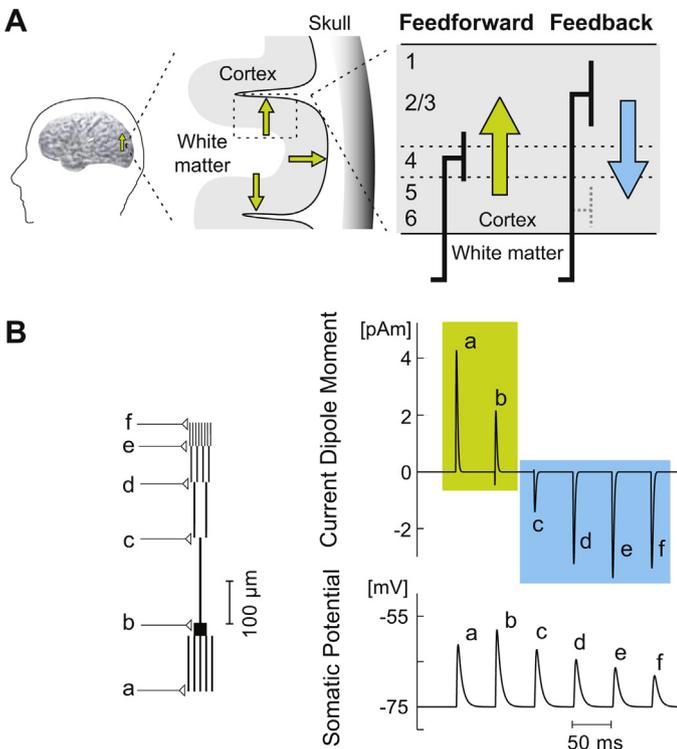


Fig. 2. Dependence of the current dipole direction on the spatial location of synaptic input.

A. Schematic illustration of the laminar distribution of feedforward and feedback synaptic input (thick lines) into a cortical area (adapted from [37]). The hypothesized direction of the resulting macroscopic current dipole is outward, i.e., away from the white matter, for feedforward input (green arrow) and inward for feedback input (blue arrow). The cross-section of a region of the cortex on the left illustrates three dipoles (small green arrows) with different physical orientations: the two dipoles depicted in the sulcal walls are tangential with respect to the skull, the middle one in the gyrus is radial; however, the physiological direction for all of these is outwards. Note that in Fig. 1B the dipoles and the cortical lamina are “upside down” compared with this laminar diagram, because those sources are located in the inferior surface of the occipitotemporal cortex.

B. A simple computational model of a pyramidal neuron to demonstrate how the direction of the current dipole can depend on the location of synaptic input. The compartmental model, built using the NEURON software (www.neuron.yale.edu/neuron/www.neuron.yale.edu/neuron/), consisted of cylindrical segments representing the soma, five basal dendrites, and an apical dendrite with a trunk and three levels of bifurcations (left). All segments were assumed to be oriented perpendicular to the cortical surface. Passive membrane properties were assumed [38]. Synaptic inputs were modeled as changes in the transmembrane conductivity in the form of the alpha function with time constant $\tau = 0.7$ ms. The synapses were placed at the end points of the dendritic segments (labeled “a”–“f”) and activated one at a time. The net current dipole was calculated by summing the dipole moment, obtained by multiplying the intracellular axial current by the length of the segment, for each segment of the pyramidal cell model [30]. When excitatory input was located at a basal dendrite or the soma, the corresponding current dipole (top) was in the upwards direction, i.e., positive values corresponding to outward currents (“a” and “b”, green), whereas for distal apical inputs the direction was reversed (“c”–“f”, blue). The change in the trans-membrane potential in the soma (bottom) was in the same direction in each case. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

interpretation, with feedforward and feedback inputs creating outward and inward currents, respectively. Thus, the direction of MEG and EEG source currents may contain information about whether the observed activity is due to inputs from a cortical area lower or higher in the hierarchical organization.

A simple model to demonstrate how the direction of the current dipole can depend on the pattern of synaptic inputs is shown in Fig. 2B. Excitatory synapses in the distal parts of the branches representing the apical dendrite of a pyramidal cell resulted in a current dipole pointing towards the white matter (negative signals

in Fig. 2B; labels c–f), whereas input close to the soma resulted in the opposite dipole direction (positive signals; labels a and b). The direction of the change in the somatic potential was the same in each case, i.e., depolarization. Similar reversal of source direction as a function of the dendritic input location has been shown previously using models with unbranched [6,23] as well as realistically-shaped [2,26] dendritic trees.

Using a detailed network model of the primary somatosensory cortex that contained many cell types in multiple layers, Jones et al. have shown that excitatory drive to different layers could create current flow in different directions [21–23,41]. The model could reproduce a sequence of outward–inward–outward directed currents (M25, M35, M50) in the MEG data with a single thalamic feedforward event that predominantly drove supragranular layer (layer 2/3) pyramidal neurons. This sequence started with excitatory current up the apical dendrites due in part to back propagation of action potentials (i.e., outward current, M25), followed by local network recruited inhibition near the somas creating inward current (M35), followed by recurrent excitation that created outward current (M50). For the later part of the somatosensory evoked response, a large early inward peak occurred at ~ 70 ms (M70); in the computational model this arose from a feedback type input to the supragranular layers that resulted in current flow down the supra- and infragranular pyramidal neuron dendrites [22,23]. This peak was dominated by the activity in the larger layer five pyramidal neurons due to their dendritic lengths. This feedback drive also created a subsequent outward peak at ~ 100 ms (M100) from recurrent excitation in the network and back propagating action potentials and a later outward peak (M135) was recreated with a second thalamic feedforward drive, as might arise from a thalamocortical loop of input. During a tactile detection task the magnitude and timing of the feedback induced peaks, M70 and M100, depended on the percept of the subject, and could be modulated with the feedback drive in the model. This result is consistent with the idea of inward currents reflecting higher order feedback inputs [11].

Inward source currents associated with top–down influence have also been reported in scalp EEG studies of object perception using fragmented line drawings or illusory contours, showing surface negative responses in ventral visual areas [13,31]. In a recent study of visual shape discrimination, late inward source currents related to target detection were found in area V4 that were consistent with feedback input from the lateral occipital region [4]. These surface negative responses were suggested to be related to the selection negativity event-related response component, which in primate recordings have been associated with attentional modulation of activity in area V4 mediated by inputs to feedback recipient layers [28]. Indeed, surface negative responses are commonly associated with top–down attentional modulatory inputs [40]. For example, although the N1 component of the auditory evoked response is considered to be “exogenous”, reflecting bottom–up influences in the cognitive sense, feedback to auditory cortex during dichotic listening tasks is observed as enhanced “negative difference/processing negativity”, reflecting enhanced inward currents, in N1 responses to attended vs. ignored responses [32].

To predict the source current direction on the basis of anatomical connections, it is essential to identify the location of the synaptic inputs with respect to the dendritic morphology of the receiving cell. For example, excitatory inputs to basal dendrites are expected to result in currents opposite to those resulting for excitatory inputs to distal parts of the apical dendrite (cf. Fig. 2B). Relating the laminar input patterns to the source current direction is challenging because only limited information about both the laminar pattern of synaptic connections and the laminar location of the soma and dendrites of the receiving neurons is currently simultaneously available [34].

The source direction also depends on whether the synaptic inputs are excitatory or inhibitory; the same spatial distribution of excitatory and inhibitory inputs would result in source currents of opposite directions [5]. The vast majority of inputs from other cortical areas is excitatory, but the ensuing activity within the local cortical circuitry is likely to involve activation of inhibitory interneurons. However, the spatial distribution and receptor properties of inhibitory synapses, in particular those of GABA_A type, give reasons to expect that they contribute less than excitatory ones to the source currents. GABA_A receptors are mostly at or near the soma [14], where the ensuing post-synaptic axial currents flow in opposite directions in the basal and apical dendrites, and the net source current largely cancels out [2,26]. Furthermore, the reversal potential of GABA_A receptors is typically close to the membrane resting potentials (shunting inhibition), and therefore, there will be little synaptic currents without simultaneous excitatory inputs. However, some contributions to the source currents can be expected from hyperpolarizing inhibitory GABA_B type synapses, which are also more distally located [14].

A prior computational modeling study investigated the impact of somatic targeting GABA_A synaptic inhibition on source currents in the context of gamma rhythms [24]. That study found that strong somatic GABA_A inhibition could induce inward-directed dipole currents. In the model, these inward currents required strong spiking and synchrony in the inhibitory neuron population, which induced fast inward current flow in the apical dendrites across the pyramidal neuron population. Similarly, strong synchronous inhibition distally in the apical dendrites induced fast outward current flow. A rapid deflection in the dipole current waveform was suggested as a means to distinguish GABA mediated influences from more diffuse excitatory synaptic influences. Under this framework, the slower deflections in Fig. 1C are more consistent with diffuse excitatory synaptic inputs. In general, multi-feature dynamic patterns of activation could potentially be used to better resolve different types of inputs, including also, for example, lateral connections between areas at the same level of hierarchy [12]. For this, intracranial recordings with multi-contact electrodes provide invaluable data for relating laminar input patterns and the MEG and EEG source waveforms [16,37].

The dependence of source direction on the type of input could provide a means for obtaining non-invasive information about the activation patterns among hierarchically organized cortical areas. Interpretation of the activation patterns in terms of hierarchical organization of the functional neuroimaging data is generally based on a priori assumptions about the hierarchical levels [12]. Relating features of the MEG/EEG source waveforms to feedforward and feedback inputs could provide unique information about the activation patterns within hierarchically organized cortical areas in the human brain.

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Author contributions

These authors SPA, SRJ, JA, JWB, and MB conceived and developed the conceptual framework. These authors SPA and MB analyzed the data. Author MSH contributed for analysis tools. These authors SPA, SRJ, JA, and MB wrote the manuscript.

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