

# Neural representation of language: activation versus long-range connectivity

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**Cognitive functions are thought to build on connectivity within large-scale neuronal networks, rather than on strictly localized processes. Yet, present understanding of neural mechanisms of language function, as derived from neuroimaging, is based on mapping brain areas that are more active during specific linguistic tasks than in control conditions. Connectivity can then be evaluated among those areas. However, network nodes should ideally be determined based on their correlated time series of activity. Recent developments in analysis methods now facilitate localization and characterization of functionally connected neural networks directly from real-time magnetoencephalography data. Analysis of long-range connectivity might clarify and expand the view provided by traditional neurophysiological and hemodynamic activation studies. Here, we use silent reading as the example process.**

## Activation versus connectivity: how to describe neural processes?

Neuroimaging studies of language processing, and of human brain function in general, typically use so-called activation paradigms. In these experiments, different types of stimuli are presented to the subject, or s/he performs different tasks on the same set of stimuli, and the brain areas that show stronger signal in the 'activation' condition versus a selected 'baseline' or 'control' condition are identified. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), using hemodynamic measures, typically seek answers in terms of where the active areas are located, whereas electroencephalography (EEG) sets the emphasis essentially on timing. Magnetoencephalography (MEG) combines accurate timing with a good estimate of the spatial distribution of active brain areas (Box 1).

However, the 'where' and 'when' descriptions are likely to provide only a partial and potentially inaccurate view of the neural implementation of language function. Cognitive functions are thought to build on connectivity within large-scale neuronal networks, rather than on strictly localized processes in the brain [1,2]. Natural language function requires an efficient interplay between sensory analysis, linguistic assessment, intention, memory search and motor output. The network concept thus seems

particularly appropriate for characterizing the cerebral implementation of human language.

Functional and/or effective connectivity between brain areas can be estimated from PET or fMRI data, based on predefined regions that are typically selected among areas revealed by contrasting levels of activation between experimental conditions [3,4]. However, time courses can be highly correlated, even when the overall activation does not exceed noise level. Furthermore, the same brain area might be equally active in both experimental and control tasks and, therefore, not evident in the resulting contrast map. Because hemodynamic techniques provide a slow and delayed signature of neural activity, evaluation of synchrony and direction of information flow between brain areas is problematic.

Spatially distributed components of cerebral networks are assumed to connect via synchronized neuronal firing [5–7]. Recent developments in analysis methods now facilitate identification of brain areas with correlated time courses of activation directly from MEG signals, without prior assumptions of network structure [8]. Thus, instead of a detour via 'where' and 'when', it is possible directly to assess the question of 'how' distinct brain areas work together to support cognitive behavior. Here, using silent reading as an example, we first discuss the views into neural organization of language function provided by traditional activation maps obtained using neurophysiological and hemodynamic imaging methods, and then consider how analysis of real-time neural networks might complement and enhance those views.

## Neurophysiological markers of silent reading: functional roles

It is usually assumed that when we see a familiar word, such as 'brain', the visual features must be processed first before the analysis can proceed to the content, apparently firstly at the level of single letters and then as a whole word, further activating the meaning of the word (semantics) and its sound form (phonology). Theoretical models of reading are based largely on analysis of behavioral reaction times and error types in acquired and developmental reading disorders. According to the influential dual-route model [9], unfamiliar words or nonwords cannot be handled by the lexical semantic route but, instead, they are processed letter by letter, converting each grapheme to its corresponding phoneme (phonological route). A

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### Box 1. Neurophysiological versus hemodynamic imaging methods

MEG enables real-time tracking (1 ms) of neuronal currents via the magnetic field that they generate; EEG detects changes in neuronal activity via the electric field. Magnetic field passes the skull and the scalp essentially unaffected. Based on the signals recorded by the MEG sensors, the sources of electric current in the brain can be determined with reasonable accuracy (1 cm). A well-established approach to solve this inverse problem is to model the active areas as focal equivalent current dipoles. Distributed models produce probability maps of current distribution. For voxel-based analysis, one can construct so-called beamformers, spatial filters that maximize the signal from one voxel while suppressing activity from other voxels.

Changes in oxygen consumption can be tracked with fMRI. The magnetic properties of hemoglobin vary with oxygenation. The ratio of oxygen-rich and deoxygenized hemoglobin is different in an active brain area than in the surrounding tissue, and these areas of different magnetization can be localized accurately (1 mm). fMRI provides a delayed (5–6 s) and temporally blurred signature of neuronal activity. In PET, increased blood flow is measured by feeding a radioactive marker substance into the circulation and forming a spatial map of activation based on the detected radiation.

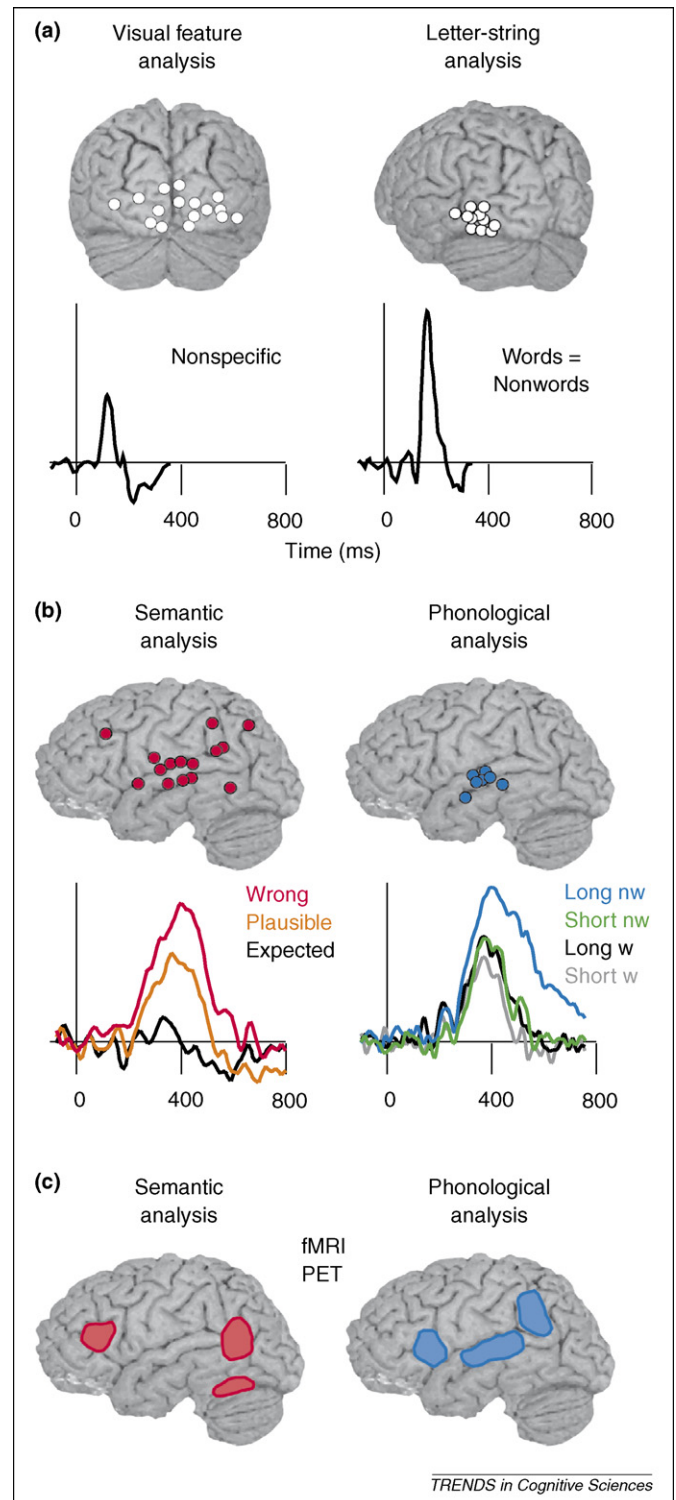
MEG and EEG are sensitive to small changes in synchrony within a neuronal population but these changes do not necessarily require increased metabolism, and thus can remain invisible in fMRI and PET recordings. However, sustained neuronal activity might go undetected in MEG or EEG, although it produces a clear fMRI and PET signal. It is currently not known whether the amount of activity or its synchronicity is more relevant to human behavior.

prominent alternative account, the distributed connectionist model [10], assumes that both familiar and unfamiliar words are handled by exactly the same network, in which orthography, phonology and semantics are processed simultaneously in a single, strongly interactive process, and it is the amount of exposure to letter strings, rather than their lexical status, that influences the behavior of the system.

The cortical dynamics of silent reading, as revealed by MEG, are summarized in Figure 1a and b. First, there is basic visual feature analysis around the occipital midline, at ~100 ms; then, 50 ms later, there is lateralization to the left occipitotemporal cortex (OT) for letter-string analysis. Reading comprehension is reflected as activation in and around the left superior temporal cortex (ST) at 200–600 ms [11].

These areas and time windows with specific functional roles form a small subset of the multiple areas that are active in the left and right hemisphere within ~1 s after word presentation. The early prelexical processing stages (Figure 1a) can be teased apart by parametrically varying noise level and length of letter and symbol strings. The occipital 100 ms response, reflecting visual feature analysis, varies with visual complexity but not with stimulus content [12]. The subsequent letter-string-specific activation, reaching a maximum at ~150 ms, signals a transition from stimulus nonspecific to category-specific analysis and, apparently, the first stage of linguistic processing. It seems to reflect prelexical analysis because the response does not differentiate between words, nonwords or consonant strings [13,14], in agreement with intracranial recordings [15].

Neurophysiological signatures of lexical semantic analysis of written words are typically determined using



**Figure 1.** Neural representation of different processing stages in single-word reading. (a) Prelexical processing in silent reading, determined with MEG. Dots represent centers of active cortical patches collected from individual subjects. The curves display the mean time course of activation in the depicted source areas. The stage of visual feature analysis in the occipital cortex (~100 ms) is stimulus nonspecific. The stimulus content starts to matter by ~150 ms, when activation reflecting letter-string analysis is observed in the left OT [12]. (b) Subsequent activation of the left ST at ~200–600 ms reflects lexical semantic analysis because its strength is affected by how well the stimulus word matches the preceding context (semantically wrong, unexpected but plausible, or expected) [17]. Activation of the left ST also seems to reflect phonological analysis because it is strongly influenced by the string length (long or short) when the stimuli are nonwords (nw) but much less when they are real words (w) [24]. (c) Cerebral loci associated with semantic and phonological analysis of written words, based on a meta-analysis of 35 fMRI and PET studies [30].

word pairs or sentences that first set a context which the target word agrees with or not (semantic priming) [16]. The level of agreement can be graded to provide more data points along the semantic continuum. Figure 1b (i) illustrates how activation in and around the left ST cortex from ~200 ms onwards is varied when subjects are reading sentences which create a very high expectation for a certain final word [17]. The activation is strongest to semantically wrong sentence-final words that require more cognitive analysis, and it is essentially nonexistent to the expected final words. A crucial finding was that semantically plausible words evoke a significantly weaker response than do the semantically wrong final words, although they are equally unexpected. This type of graded response is generally taken to reflect lexical semantic processing, an interpretation supported by studies in which the lexical semantic properties of single words or word pairs have been carefully manipulated [18–20]. When the active areas are modeled as focal sources (Box 1), the activation sensitive to lexical semantic manipulation is consistently localized to the ST cortex [14,20–22]. Distributed models suggest further spreading of activation to the anterior temporal cortex (AT) and inferior frontal cortex [21,23].

Activation of the same general brain area, in the same time window, also seems to reflect phonological analysis. Figure 1b shows the activated areas and time course of activation for reading short (four-letter) and long (eight-letter) words and nonwords [24]. The dual-route model of reading predicts that, for real words, the lexical route dominates and, in this case, the word length has little effect. Processing of nonwords, however, would rely on the letter-level grapheme-to-phoneme conversion and subsequent phonological processing. Nonword length should thus have a strong effect on the amount of phonological processing required. The MEG data show a remarkably similar response to short and long real words. However, the long nonwords evoke an activation that is significantly stronger and lasts twice as long as that for the short nonwords [22,24]. If one accepts the dual-route model, this result implies that both semantic and phonological processing are reflected in the left ST activation at 200–600 ms poststimulus. Does the spatial distribution of these neurophysiological markers of letter-string, lexical semantic and phonological analysis agree with that observed in hemodynamic studies?

### Neurophysiological versus hemodynamic view of reading

Both neurophysiological and hemodynamic imaging studies indicate that in the left inferior OT there are neurons that show letter-string-specific activation [12,15,25], and that such activation is abnormally weak in dyslexic individuals, who have difficulties in learning to read and write [14,26,27]. Despite this apparently compelling agreement between the imaging methods, there are discrepancies in both anatomy and function: (i) the source area determined from MEG data seems to be located posterior and medial to the center of the hemodynamically determined maximum [14]; (ii) the neurophysiological response does not differentiate between real words, nonwords or even consonant strings, whereas hemodynamic

studies report significantly stronger activation to real words than to consonant strings [28,29]. One plausible way to reconcile the findings is to assume that MEG detects the onset of letter-string-specific analysis which is not detected in, or does not dominate, the hemodynamic signal. fMRI or PET would detect subsequent activation along the ventral stream, where neurons would be increasingly sensitive to the word-likeness of the letter strings but would show weaker synchronization or be less rigorously time locked to stimulus presentation and might thus go undetected in MEG [13,14].

Semantic processing, based on a meta-analysis of 35 fMRI and PET studies on reading [30], is consistently associated with activation of the triangular part of the inferior frontal gyrus, posterior middle temporal gyrus and basal temporal cortex, whereas phonological processing is reflected in activation of the ST cortex, supramarginal gyrus and opercular part of the inferior frontal gyrus (Figure 1c). Agreement between MEG and fMRI or PET findings is not impressive. The left ST cortex is implicated in phonology by both MEG and hemodynamic measures but only MEG consistently assigns it a role in lexical semantic analysis. For this particular discrepancy, one could consider a rather simplistic account; in fMRI and PET studies, based on the dual-route model of reading, areas involved in phonological analysis are thought to be revealed by subtracting activations to real words from those to nonwords. Areas involved in semantic processing, however, would be sought by the inverse subtraction. Based on the MEG data, such subtractions would indeed show stronger activation of the left ST to nonwords than words (phonology) but no activation that would be stronger for words than nonwords (semantics); this would be the case if both semantic and phonological manipulations affect essentially the same neuronal population.

Considering that language processing is likely to be implemented in the form of long-range connectivity within extensive neural webs, one might wonder if the apparent variability in functional localization between imaging methods (and, possibly, between individual subjects) partly reflects the way that each method and analysis approach happens to probe the underlying network structure. Therefore, it seems essential to characterize the networks – that is, the underlying connectivity structure as a whole, and not only changes of activation.

### Real-time connectivity during reading

When the time courses of neural activity in specific areas are known, there are mathematical tools available for evaluating connectivity and direction of information flow between those areas (Box 2). However, conversion from MEG or EEG sensor or electrode-level measures to actual locations and time courses of activity at the level of the brain is problematic (Box 1). The complexity of the problem increases enormously when one wishes to identify not just activity in specific areas but within pairs and, eventually, networks of areas that display correlated time series of activation. Because of this, coherence analysis in cognitive tasks has, so far, been limited to the level of EEG electrodes or MEG sensors, without reference to the actual source areas in the brain [2,31,32].

### Box 2. Measures of neural connectivity

- **Correlation** is a measure of similarity between amplitudes of two time series.
- **Cross-correlation** further includes information on systematic time shifts between the two time series.
- **Cross-spectral density** can be calculated by multiplying the Fourier-transformed signals (frequency space) of the time series.
- **Coherence** is obtained by normalizing the cross-spectral density with the power spectral density of both time series. Its value ranges from 0 (no similarity) to 1 (identical time series).
- **Similarity of signal phase** is frequently thought to be a more relevant measure of neural synchrony than is cross-correlation or coherence, which are also influenced by the possible interaction of the amplitude changes in the signals [2].
- **Phase locking** occurs when the instantaneous oscillatory phases display a constant relationship over multiple cycles [2,7,43].
- **The synchronization index** is a measure comparable to phase coupling that uses the Hilbert transform [44].
- **The directionality index** [45] estimates uni- versus bi-directionality between instantaneous phases of two time series.
- **Granger causality** estimates the causality directly between two time series, not their phases [46] (for application to fMRI data, see Roebroeck *et al.* [47]).

Recently, an analysis tool has been introduced [Dynamic Imaging of Coherent Sources (DICS)] [8] that determines real-time long-range networks directly from MEG data (Box 3). When relevant peripheral data are available to serve as an initial reference signal, such as muscle activity in motor tasks [33], the analysis can be fairly straightforward. In cognitive tasks, however, there are usually no meaningful nonbrain reference signals to seed the analysis. Here, one can proceed as follows [34]: (i) correlation of time courses of activation is calculated for all voxel pairs, for computational feasibility in a part of the brain (e.g. left-hemisphere cortex), and tested for significance; (ii) voxels with the highest number of connections to other voxels are taken as initial reference areas; (iii) starting from these areas, network nodes are searched in the entire brain; (iv) connectivity between all identified nodes is quantified (Box 2) and tested for significance.

Because connectivity analysis only relies on timing at the neuronal level, it facilitates the use of continuous, increasingly realistic tasks that the human brain is tuned for. Figure 2 displays a left-hemisphere network of densely interconnected areas during rapid serial visual

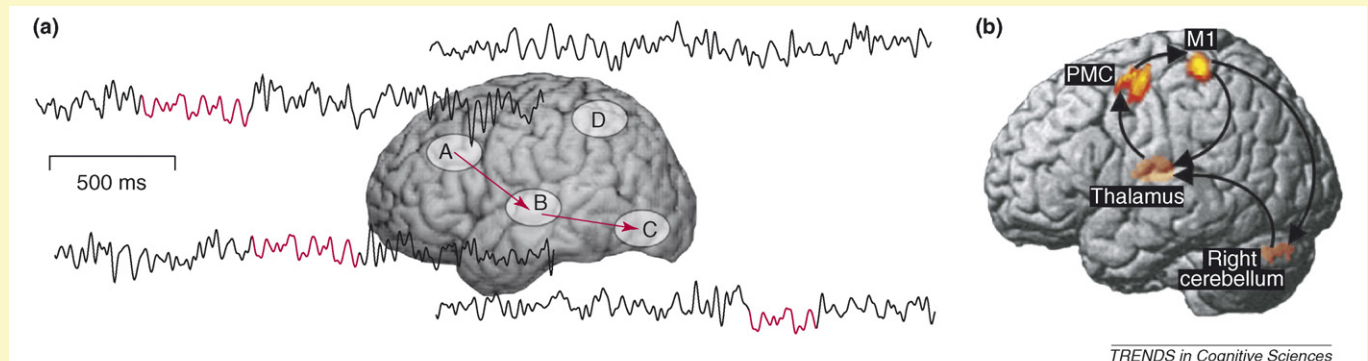
### Box 3. Extracting real-time neural networks from MEG data

When two brain areas are functionally connected, one would expect to observe similar time courses of activation in those areas, at least transiently. Figure 1a displays a simplified version of this basic idea. A stretch of data (segment in red) recorded from area A is repeated, somewhat delayed, in area B. Part of that signal is also recorded from area C, shifted even further in time. The time course of activation in area D does not share signal features with activation in the other areas. Based on such data, one could reasonably suggest that neural activity in area A drives that in area B, directly or via another area, and there is a weaker drive further to area C.

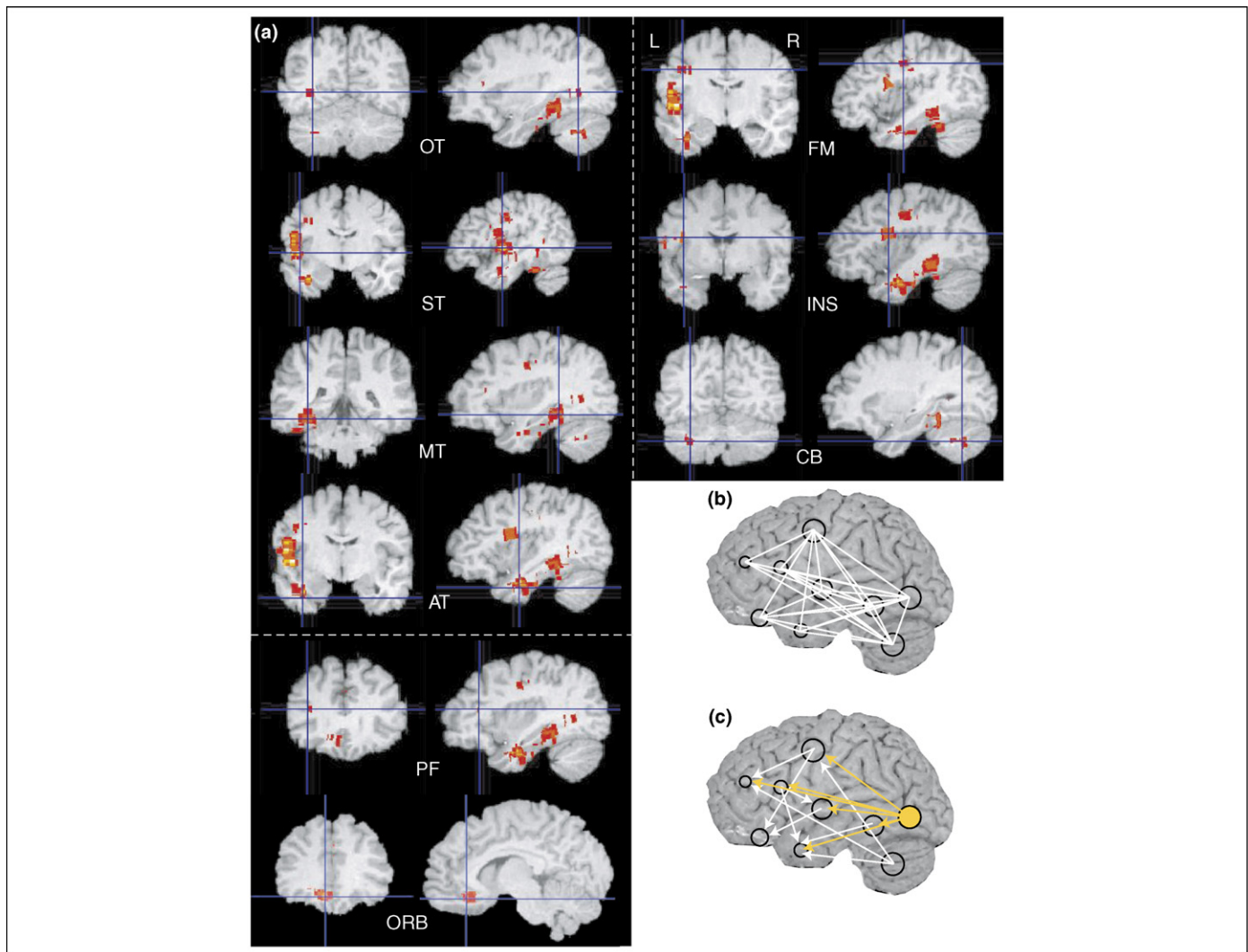
DICS [8] extracts real-time long-range connectivity between brain areas directly from MEG data. The time series recorded by the MEG sensors are transformed into the frequency domain by computing cross-correlation spectra for all sensor combinations. Because cross-correlation spectra retain the signal strength and phase (timing) relationships among the sensor sites, the brain areas generating the signals can be localized. A spatial filter (Box 1) optimized for the frequency domain enables focusing on the

activity of one brain area while suppressing activity from other areas.

Although, ideally, one would like to evaluate connections between all voxel pairs in the brain and test them for significance, currently this is not feasible within a reasonable amount of time. Therefore, a crucial step in the analysis is to identify some node(s) of the network, which can then be used as initial reference areas to find other nodes. A meaningful peripheral signal might help in finding a starting point in the brain. Figure 1b depicts a cortical network identified during performance of slow finger movements [48]. Here, the search started from the electromyogram (EMG) recorded from the moving right index finger. Correlation between the EMG and the MEG sensor signals highlighted the contralateral motor cortex, which was used as reference area in the subsequent search for connected areas within the brain (MEG-MEG coherence). The DICS analysis revealed a reverberating loop involving the left motor and premotor cortex, left thalamus and right cerebellum. Because of a well-defined characteristic frequency of the movement (6–9 Hz), it was possible to obtain estimates for direction of information flow between the nodes (arrows in Figure 1b).



**Figure 1.** Extracting long-range neural connectivity from MEG data. (a) Simplified presentation of the basic idea. Curves depict time courses of activity in four brain areas (gray ellipses). If neuronal populations in these areas are functionally connected, one would expect to detect similar time courses of activation in the different areas (red segments), at least occasionally. Time shifts between similar stretches of activity could be interpreted as flow of information. In this example, one could argue that there is a drive from area A to B and a weaker drive further to area C. Delays between the repeated segments are exaggerated. (b) Neural network during slow movements of the right index finger. Here, EMG from the moving finger provided a meaningful, nonbrain reference signal. EMG-MEG coherence led to the contralateral motor cortex, which served as a reference area for identification of the network within the brain. Abbreviations: M1, primary motor cortex; PMC, premotor cortex. Reproduced, with permission, from Ref. [48].



**Figure 2.** Long-range neural connectivity at 8–13 Hz during reading. (a) Group-level nodal points of the network shown on coronal and sagittal views. (b) Overall connectivity structure, with the nodes displayed on surface rendering. The sphere size represents the number of connections to and from that area. (c) Arrows indicate the connections with a dominant direction of information flow, estimated with Granger causality. OT (in yellow) emerged as the main forward-driving node of the network. Modified, with permission, from Ref. [34].

presentation (RSVP) of connected text [34]. RSVP simulates natural reading but without the need for making saccades. The network nodes form an interesting compilation of areas reported in earlier activation studies using fMRI or PET and MEG, and in intracranial studies. Activation of the left inferior OT and ST is systematically found in both neurophysiological and hemodynamic neuroimaging studies of reading (see above). Intracranial studies, however, suggest that medial temporal cortex (MT) and AT are involved specifically in comprehension [35].

Intriguingly, the network also includes nodes that, in activation studies, have been associated primarily with language production rather than perception, such as the insula (INS), face motor cortex (FM) and the cerebellum (CB) [36–38]. Moreover, the network encompassed the orbitofrontal cortex (ORB) and the left prefrontal cortex (PF), which have not been reported specifically in reading tasks but, rather, in experiments focusing on visual recognition and working memory [39,40].

Most connections seemed to be bidirectional (feedforward and feedback). The exceptional predominance of feedforward direction of information flow from OT to most of the

other nodes (Figure 2c) thus emphasizes the importance of OT as the main entrance point from visual analysis to the language network. This finding makes it all the more understandable that functional underdevelopment of the left OT area, consistently reported in dyslexic individuals, might indeed severely impair the normal reading process.

The network found by Kujala *et al.* [34] did not include the supramarginal gyrus or posterior ST, which are thought to be involved in grapheme-to-phoneme conversion [30]. The rapid reading process probably relied more heavily on lexical semantic than on phonological analysis.

## Conclusion

The spatiotemporal pattern of areas that show more activation in one condition than in another, and spatial distribution of areas that show correlated time courses of activation, provide different views into brain function. Intuitively, one might assume that the connectivity pattern represents the more fundamental underlying structure which becomes partially (or fully) discernible in activation studies. Silent reading should be a good cognitive task for illustrating these different views because

of the relatively large quantities of both neurophysiological and hemodynamic data available, and also theoretical models for consideration. MEG and fMRI or PET activation studies have associated somewhat different brain areas with specific subprocesses of reading, possible reasons for which were briefly discussed earlier and in **Box 1**. Interestingly, the MEG connectivity analysis revealed a set of nodes that essentially encompassed the areas defined as active in MEG, PET and fMRI studies. Furthermore, the connection analysis highlighted a close interplay among a set of areas typically associated with speech production and visual recognition, thus emphasizing a global nature of language processing, in agreement with the view recently advocated by an extensive meta-analysis of hemodynamic activation studies [41].

As regards models of reading, the activation data discussed above would seem to point to involvement of a single network in reading, rather than spatially dissociable routes for processing words and nonwords. Such a view might lend support to the connectionist model; note, however, that the dual-route model does not make specific predictions of spatial dissociation at the level of the brain. In contrast, the systematic changes of activation strength and duration in the left ST by letter-string length and lexicality would agree with the dual-route account. The connectionist view, even in its modified form [42], locates the effects of length and lexicality at the visual input and articulate output levels, not in the core linguistic processes, as suggested by the neural data. Connectivity analysis could help to clarify this mixed picture. A recent fMRI study suggests that word versus nonword reading is associated with specific changes of effective connectivity [3]. However, the question remains whether it is sufficient to test for connectivity between areas that have been

identified by contrast analysis in activation studies, or whether the picture would be crucially altered if the initial selection of the network were to be based directly on neural connectivity. The MEG-based coherence analysis can hopefully help to elucidate these issues, using, for example, paradigms which systematically vary the need for lexical versus phonological analysis of written text.

This new line of research is currently in its early stages, and there are multiple intriguing aspects that need to be examined before full application to detailed neuroscience questions (**Box 4**). For a comprehensive picture of human brain function, it will be essential to understand and capitalize on the similarities and differences between hemodynamic and neurophysiological measures. Analysis of cooperation between different brain areas, derived directly from neuroimaging data, is a crucial step in this endeavor.

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#### Box 4. Questions for future research

- What is the correspondence, in individual subjects, between brain areas identified as nodal points in network analysis, and areas showing a task-specific increase in activation? Do they coincide or are they systematically shifted in location?
- What is the correspondence between functional long-range connectivity mapped with DICS and anatomical connectivity mapped with diffusion tensor imaging (DTI) of white matter tracts? The nodes of the functional network should serve as excellent seed points for DTI analysis, which could again feed back to the functional analysis. For example, starting from the left inferior OT node, would white matter tracts lead to FM, directly or indirectly?
- How similar are the long-range networks derived from neurophysiological (MEG) and hemodynamic (fMRI) recordings, at the individual level? If MEG and fMRI data were collected for the same experimental paradigm, and the network nodes determined directly from MEG time courses and introduced as nodes into Dynamic Causal Modeling (DCM [3,4]), would the emerging internal structure of the network be essentially the same?
- How specific are the networks to the task, and input and output modality? By comparing, for example, reading, speech comprehension, calculation and bimanual handling of an object, can one identify task-specific components of the networks and also network nodes common to all or most tasks, with connectivity (possibly) modulated by the different tasks?
- If the existence of task-nonspecific ‘default’ networks is demonstrated, to what degree is their structure (and that of task-specific networks) influenced, for example, by handedness, gender or native language?

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