Let the Rhythm Guide You: Non-invasive Tracking of Cortical Communication Channels

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In this issue of *Neuron*, a study by Michalareas et al. (2016) uses magnetoencephalography (MEG) to characterize the hierarchical organization of human visual areas based on their causal connectivity profiles.

The remarkably efficient information processing capabilities of the human brain depend on an intricate anatomical structure and dynamically coordinated interactions of specialized neuronal populations that have both been particularly well studied in the visual system. These studies suggest that a hierarchical organization shapes the interactions of specialized neuronal populations. Anatomically, laminar distributions of connections distinguish feedforward and feedback directions. Functionally, neurons in low-level visual areas are sensitive to simple features that become increasingly more complex with increasing levels of the visual hierarchy. However, the idea that simple visual features are extracted in V1 and transmitted through a feedforward pathway for transformation and selection is simplistic. Modern theories need a more flexible conception of hierarchies whereby dynamic interactions with higher-order visual areas, multi-sensory areas, and the primary sensory areas of other sensory modalities modulate information processing in early visual areas. To unravel the underlying principles shaping these interactions, we benefit from increasingly more precise anatomical and functional information about the mechanisms of feedforward and feedback communication in cortical areas.

We now have better knowledge of the anatomical routes constraining the mechanisms of feedforward and feedback cortical communication across the six cortical layers within and between the areas of the visual processing hierarchy (Markov et al., 2014). However, we are just beginning to uncover the functional signatures of feedforward and feedback information flow.

In this issue of *Neuron*, Michalareas et al. (2016) address this issue by combining detailed measures of anatomical and functional connectivity to derive a hierarchical organization of visual areas within which they reveal the functional signatures of feedforward and feedback information flow (Michalareas et al., 2016).

In this elegant, innovative study, Michalareas et al. (2016) start from a recent model of directed anatomical connectivity of macaque visual cortex based on the quantitative analysis of retrograde tracers (Markov et al., 2014). The model quantifies hierarchical distance with a single measure (fraction of supragranular labeled neurons [SLN]) that captures the laminar distribution of anatomical connections between areas (Figure 1A, left panel). SLN capitalizes on the fact that feedforward projections typically start in supragranular layers and terminate in layer 4, whereas feedback projections predominantly start in infragranular layers and terminate in layers other than layer 4. High SLN values therefore indicate a feedforward connection, whereas low SLN values indicate a feedback connection.

In seven visual cortical areas, Michalareas et al. (2016) compared this directed anatomical connectivity from macaque to a measure of functional connectivity between the homolog areas in humans. Michalareas et al. (2016) estimated interareal directed connectivity from magnetoencephalography (MEG) recordings. MEG uses highly sensitive sensors operating at −269°C to non-invasively record the tiny magnetic fields associated with neural activity. State-of-the-art systems record these magnetic fields simultaneously at 200–300 locations. To induce both bottom-up and top-down neural signals, Michalareas et al. (2016) engaged participants in a visual task with strong sensory stimulation that required sustained attention, while they recorded MEG signals. Then Michalareas et al. (2016) used the recorded MEG signals to estimate, with millisecond temporal resolution, neural activity at each of the seven selected visual areas. Finally, with Granger causality (GC), the authors estimated the directed connectivity between all combinations of the seven areas. Granger causality quantifies how much the knowledge of the past of MEG signal improves predictions of the future of another MEG signal. Michalareas et al. (2016) computed GC for each frequency between 1 Hz and 140 Hz to account for the fact that brain oscillations at different frequency bands originate from different neurophysiological mechanisms and are differentially modulated by cognitive tasks and pathological states (Wang, 2010; Schnitzler and Gross, 2005). More recently, invasively recorded data in animals (see Fontolan et al., 2014 for human data) suggested that oscillations in distinct frequency bands support feedforward and feedback signaling (Bastos et al., 2012; Fries, 2015; Wang, 2010). Michalareas et al. (2016) contribute by comparing the Granger causality spectra of anatomically defined feedforward and feedback connections. Indeed, Michalareas et al. (2016) report a spectral asymmetry where GC at ∼60 Hz frequencies (the so-called gamma band) is stronger for feedforward than feedback connections (Figure 1A, right panel shows

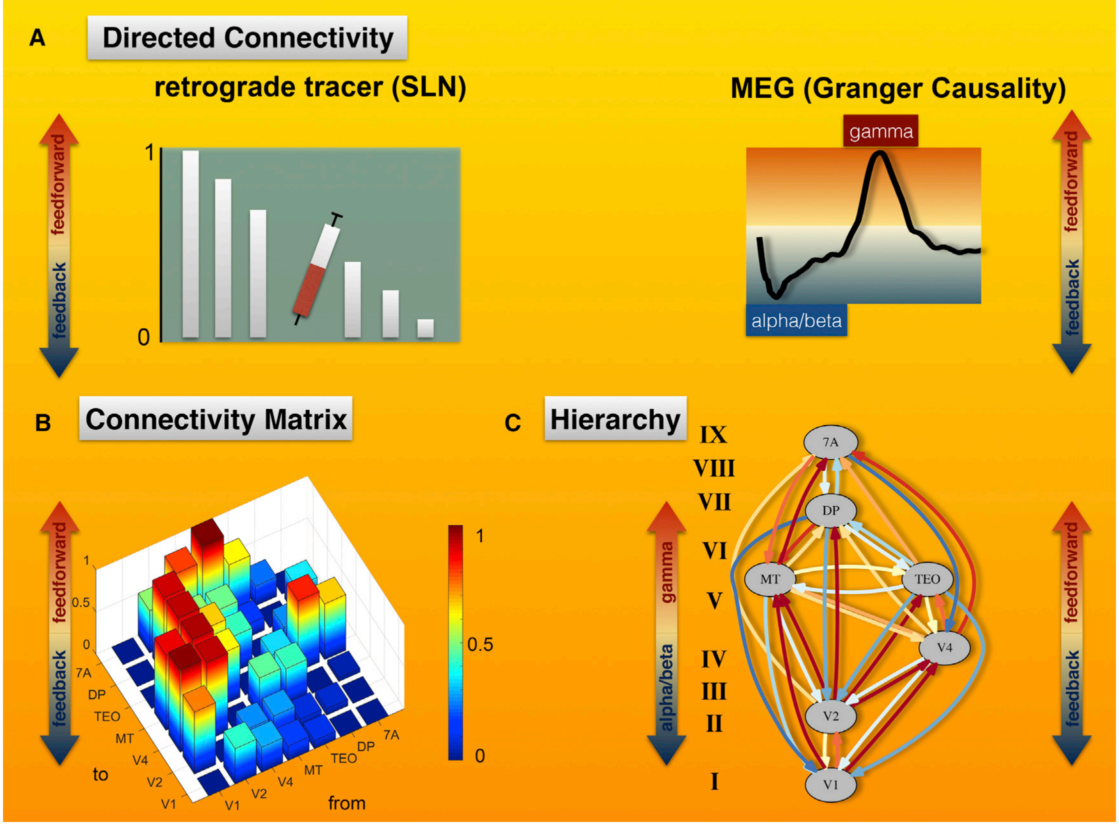

Figure 1. Reconstruction of Cortical Hierarchies from Anatomical and Functional Causality

(A) Left: directed anatomical connectivity can be estimated from the fraction of supragranular labeled neurons (SLN). Bar graph schematically represents SLN values for areas with increasing feedforward characteristic (moving leftward from injection site) and with increasing feedback characteristic (moving rightward from injection site). Right: Granger causality (GC) spectrum reconstructed from Michalareas et al. (2016). GC spectrum represents the difference of GC spectra for anatomically defined feedforward and feedback connections averaged across both hemispheres. Positive GC for gamma frequencies indicates dominance in feedforward direction. Negative GC for alpha/beta frequencies indicates dominance in the feedback direction.

(B) Anatomical connectivity matrix for selected areas with SLN values from Markov et al. (2014).

(C) Hierarchical model of seven selected visual areas. Color coding of arrows is based on SLN values from Markov et al. (2014) where blue indicates feedback and red indicates feedforward direction.

difference of GC spectra between feedforward and feedback connections averaged across both hemispheres). In contrast, GC at low 10–20 Hz frequencies (covering the so-called alpha and beta band) was stronger for feedback than feedforward connections. These findings are commensurate with previously reported results. For example, the same lab reported a similar spectral asymmetry using electrocorticography (ECoG) in two macaque monkeys in a visuospatial attention task (Bastos et al., 2015). Michalareas and colleagues expanded on this earlier study and tested whether anatomical asymmetry from macaques predicts human GC asymmetry between two areas. For each frequency and across all pairs of areas, they tested the relationship between normalized GC asymmetry and SLN values and found significant correlations in the alpha/beta and the gamma frequency bands. As expected, correlations were negative in alpha/beta band, indicating feedback directionality, but they were positive in gamma band, reflecting feedforward directionality.

This correspondence between human MEG connectivity and macaque anatomical connectivity should in principle allow for the reconstruction of functional visual hierarchies based on GC asymmetry between all pairs of areas. Indeed, this is what Michalareas et al. (2016) demonstrate in this study. Interestingly, the MEG-derived functional hierarchy of visual areas corresponds to the macaque anatomical hierarchy (Figures 1B and 1C). Finally, Michalareas et al. (2016) extended their analysis from the original set of 7 selected areas to 26 visual areas. As before, they performed the analysis separately for each of the 43 participants, allowing them to quantify consistency of the estimated hierarchies across participants. Again, results were consistent across the group and in general agreement with anatomical and functional models.

Overall, this is a remarkable demonstration that previously reported spectral asymmetries for feedforward and feedback signaling are observable in non-invasively recorded data and enable the reconstruction of cortical hierarchies.

A coherent model emerges from this and previous studies. Within cortical areas, low-frequency (alpha, beta) rhythmic synchrony seems to be stronger in deeper layers compared to superficial