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Quantitative Analysis of Connectivity in the Visual Cortex: Extracting Function from Structure

JULIEN VEZOLI, ARNAUD FALCHIER, BERTRAND JOUVE, KENNETH KNOBLAUCH, MALCOLM YOUNG, and HENRY KENNEDY

It is generally agreed that information flow through the cortex is constrained by a hierarchical architecture. Lack of precise data on areal connectivity leads to indeterminacy of existing models. The authors introduce two quantitative parameters (SLN and FLN) that hold the promise of resolving such indeterminacy. In the visual system, using a very incomplete database, provisional hierarchies are in line with the recent proposal of higher functions of area V1 and suggest a hitherto unsuspected central function of the frontal eye field. *NEUROSCIENTIST* 10(5):476–482, 2004. DOI: 10.1177/1073858404268478

KEY WORDS *Model, Primate, Connectivity, Vision*

Understanding how the cerebral cortex processes information is a major aim of neurobiology today with important implications ranging from psychiatry to the designing of living machines. Numerous techniques are used to this end including functional brain imaging, single-unit recording, and anatomy. These techniques rapidly converge at the level of the cortical area, where specific physiological functions can be localized and each area exhibits distinct patterns of connectivity. The concerted action of multiple areas is thought to underlie sensory processes and cognitive function. This has led to a major field of research that attempts to determine the position of individual areas in the overall cortical organization. Work in the visual system has been particularly fruitful in this respect. Here, Hubel and Wiesel in the 1970s built on a tradition going back to Hughlings Jackson that shows that early visual areas are organized in a hierarchical fashion. Their work suggests that as one progresses from the primary area, area V1, to successively higher areas (V2, V3, V4, etc.), there is a progressive increase in both the dimensions and the complexity of receptive fields. This hierarchical organization was at first supported by evidence that connections linked adjacent cortical areas. However, as the sensitivity of tract-tracing techniques has improved, it has become increasingly clear that individual areas interconnect with many more (8–10) than one cortical area, suggesting a highly distributed system with parallel pathways running through the hierarchical order. These results coupled

with the demonstration that specific attributes such as color, movement, and depth are emphasized in particular areas made it very difficult to develop a clear consensus of the organization of cortical areas.

The laboratory of Pandya provided a valuable clue to the anatomical arrangement of areas in the cortex (Rockland and Pandya 1979). He noted that rostral-directed projections originated from the supragranular layers and terminated in the target area in layer 4. This contrasted with caudal-directed projections that stem from infragranular layer neurons and terminate outside of layer 4. These findings were particularly suggestive because in the visual system the rostral-directed projections followed the outward sequence of areas V1, V2, V3, and so on, and therefore seemed to be a substrate of an ascending pathway. The inverse pathway corresponded to a descending pathway and further showed homology to a well-known descending pathway, namely, the corticothalamic pathway that originates in layer 6.

Hierarchical Models of the Cortex

Ascending and descending pathways were increasingly thought of as feedforward and feedback projections linking cortical areas and providing the substrate for bottom-up and top-down processing. Importantly, the work of Helen Barbas's group has shown that this concept also applies to the frontal cortex (Dombrowski and others 2001). A major breakthrough came from the work carried out in Van Essen's laboratory that made an exhaustive hierarchical analysis of cortical connectivity so as to generate a functional map of the visual system (Felleman and Van Essen 1991). To obtain this model of the visual system, they formed an extensive database from published reports in which they classified pathways between pairs of areas as feedback and feedforward according to the laminar characteristics of the pathways as outlined above. This pairwise comparison enabled them to propose a hierarchical model of the visual system (Fig. 1A). The model of Felleman and Van Essen reveals basic structure that had been established

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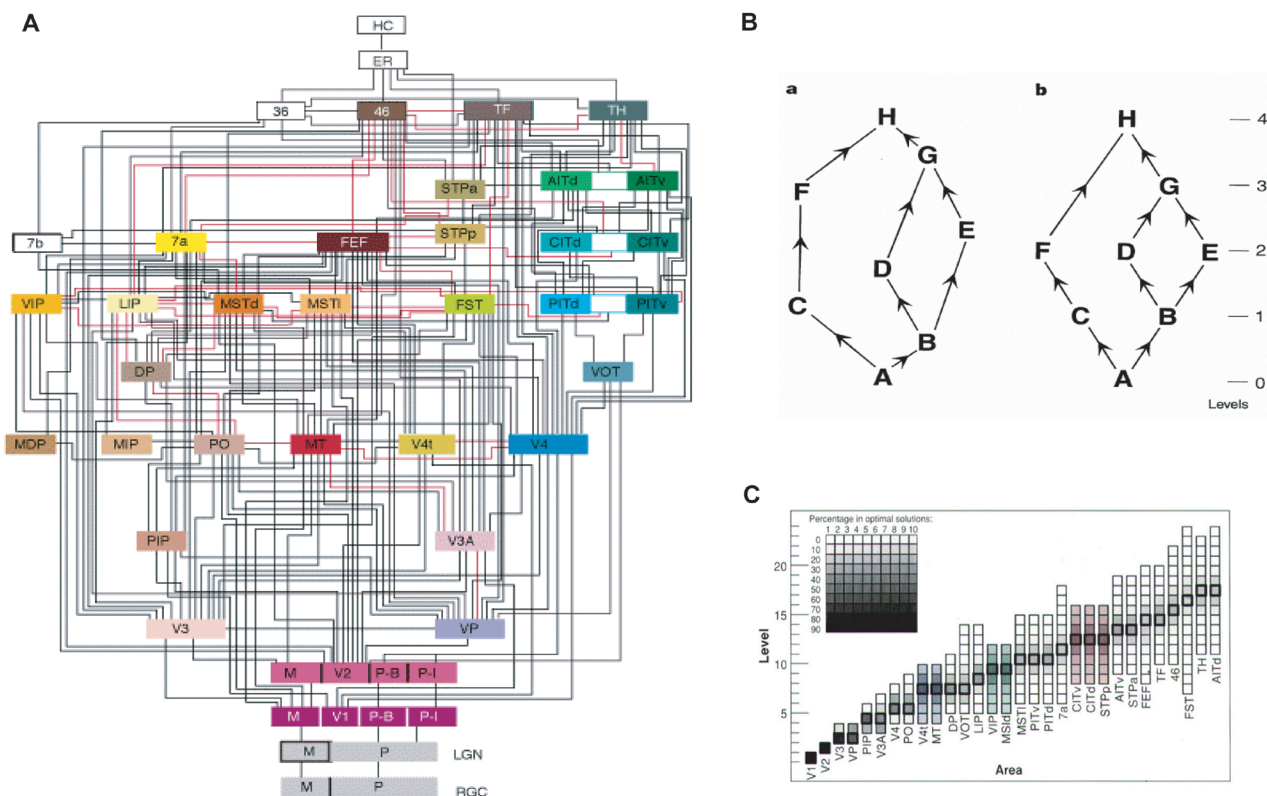


Fig. 1. Indeterminacy of existing models of the visual cortex. **A**, Felleman and Van Essen's (1991) model of the visual cortex. **B**, Parallel pathways with an absence of distance value between stations leads to a multiplicity of possible models (taken from Crick and Koch 1998). **C**, Area frequency distributions for 150,000 optimal hierarchical orderings (Hilgetag and others 1996). Much of the indeterminacy comes from the impact of an absence of a distance value on parallel pathways as shown in **B**.

by physiological studies. It revealed an orderly progression marching out from V1, V2, V3, to the prefrontal cortex, and the hippocampus and an absence of strong loops, a suggestive signature of a hierarchical system (Crick and Koch 1998) (Fig. 1B). As a map of the cortex, the Felleman and Van Essen model has been successful. However, although the concept of hierarchy was readily accepted, there was soon speculation on the extent to which the hierarchy could be determined by such procedures. Essentially, the Felleman and Van Essen model placed cortical areas arbitrarily on successive levels. This leads to several problems because the distance between levels was not known. The group of Malcolm Young investigated the extent of these problems. Using a computational approach, they showed that the Felleman and Van Essen database led to 150,000 equally plausible hierarchies (Figure 1C) (Hilgetag and others 1996). In other words, although the visual cortex is clearly organized in a hierarchical manner, there was no indication as to the functional organigram governing the flow of information through the cortex.

The publications that were used to compile the database of Felleman and Van Essen characterized projections on the basis of the laminar location of the parent cell of the projection and/or the laminar location of termination in the target area. It had been noticed that parent cell origin of a cortico-cortical connection alone is a

good indicator of feedforward or feedback category (Kennedy and Bullier 1985). This was explored in a recent study in which retrograde tracers were placed in areas V1 and V4 in the monkey. After the appropriate survival period to allow retrograde transport of the tracer, the laminar distribution of labeled neurons was examined. This showed that after an injection in area V4, areas hierarchically lower than V4 showed progressively more labeled neurons in supragranular layers reaching 100% in area V1 (Fig. 2). The converse was true in that increasing hierarchical status revealed that progressively more labeled neurons occur in infragranular layers. The percentage of supragranular layers is referred to as the SLN, and in fact a single injection in area V4 gave a smooth increase in SLN in the descending hierarchical series going back V3, V2, and V1. Likewise there was a similar smooth decreasing value of SLN in the ascending hierarchical series (Barone and others 2000). The fact that the values of SLN are graded and continuous is particularly interesting because it suggests that this index may be directly related to hierarchical distance. In fact, a single injection of area V4 was sufficient to accurately determine the hierarchical relations of the areas projecting to area V4.

The predictive power of SLN was unexpected. Numerous studies had looked at the laminar distribution of cortico-cortical neurons and had failed to identify it

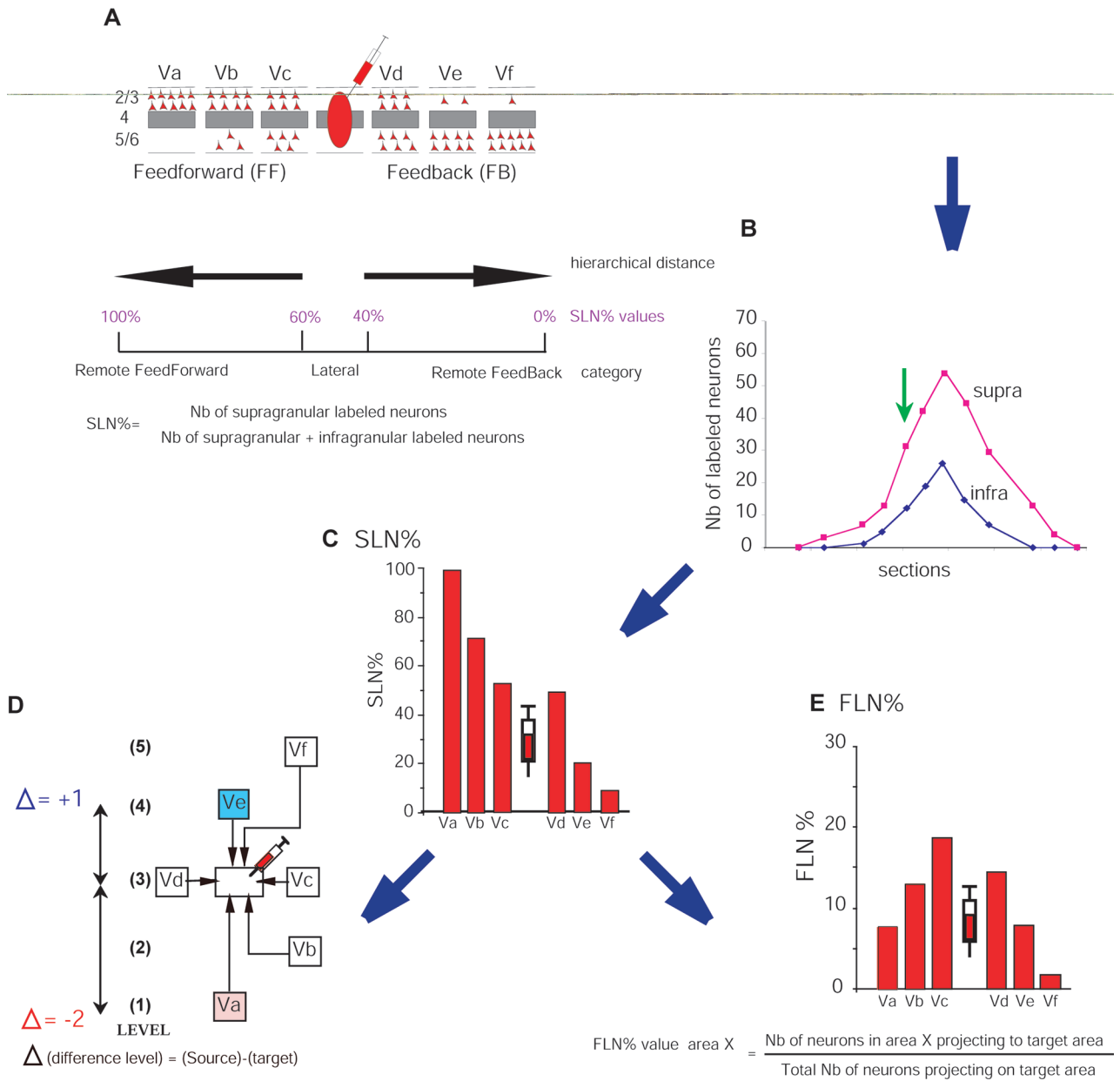


Fig. 2. How to extract SLN and FLN from feedforward and feedback connections. **A**, Diagram illustrating the distribution of labeled neurons in feedforward and feedback projections after injection of tracer in the target area. Each area has a specific SLN value, which determines its hierarchical distance from the target area. Remote feedforward projections (e.g., Va) have SLN values of 100%. More proximal feedforward areas have lower SLN values. Remote feedback projections have SLN values of 0 (e.g., Vf). More proximal feedback areas have higher SLN values. SLN values of 60% to 40% correspond to lateral connections. Because of cortical curvature and the nonuniform distribution of labeled neurons in the projection, stable values of SLN require examining the distribution of labeled neurons at closely spaced intervals. Counts of neurons on successive sections show density profiles (**B**), the smoothness of which indicates appropriate sampling frequency. Each area returns specific SLN values (**C**) (Batardiere and others 1998). **D**, Hierarchical model of cortical areas connected to the target area according to the relationship between the SLN% and the distance rule (Barone and others 2000). **E**, Total number of projection neurons is calculated for each area. This makes it possible to calculate the relative contribution of each area to the total afferent connectivity of the target area.

with hierarchical distance. One reason for this reflects the difficulty in accurately identifying the correct value of SLN. This partly arises from laminar distortions due to curvature of the cortex and is partly due to the fact that retrogradely labeled neurons are unevenly distributed in the projection zone in the source area (Batardiere

and others 1998). Labeled neurons in the projection zone peak at a central core region and gradually decrease toward the periphery of the projection zone. Furthermore, the gradient is sharper for supragranular layer neurons than for infragranular layer neurons; hence, the infragranular layer neurons tend to stretch fur-

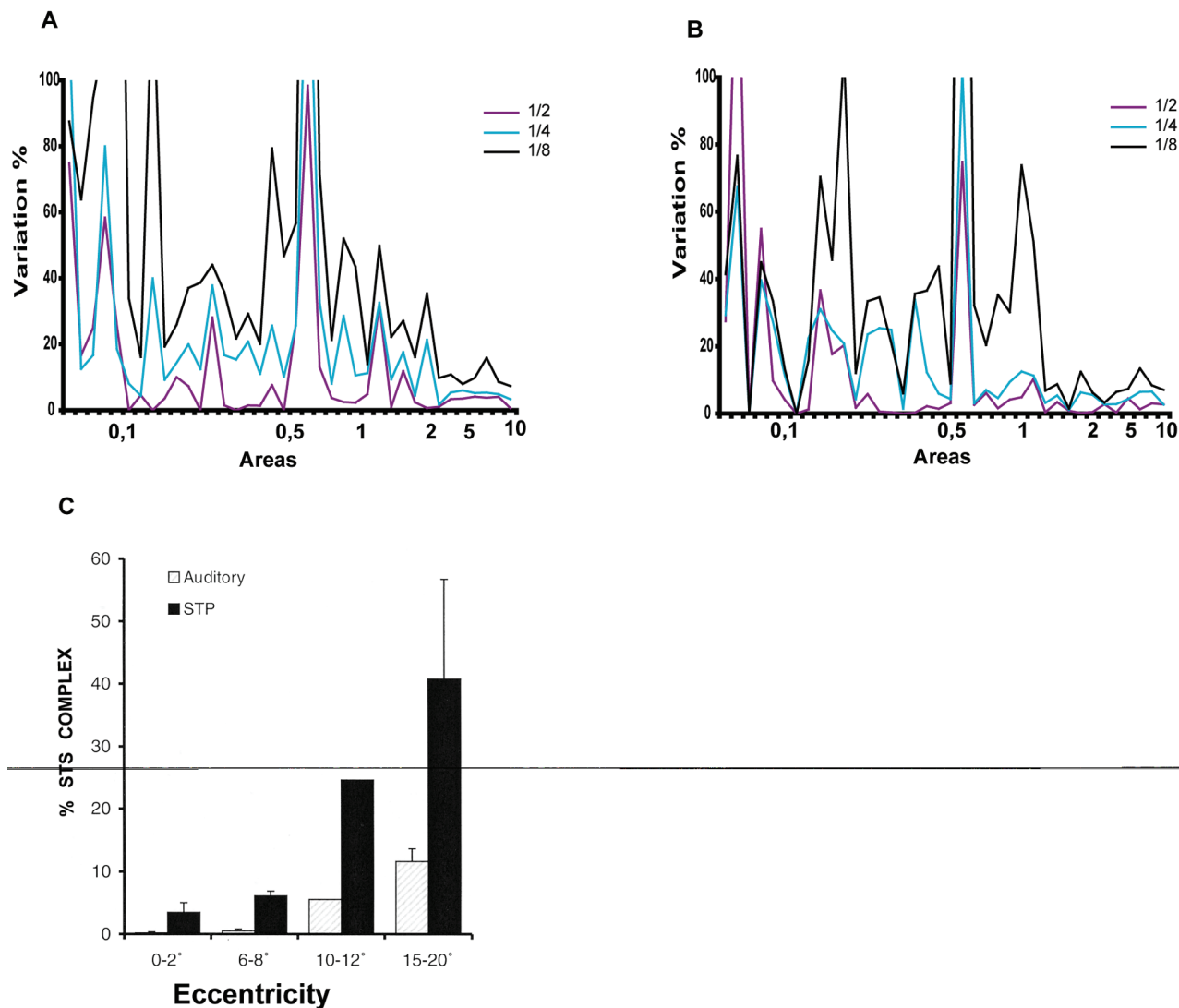


Fig. 3. Effect of sampling frequency on variability of SLN and FLN. *A*, Variation of FLN% for the 50 cortical areas projecting to area 45. FLN values of the cortical areas are indicated on the horizontal axis. FLN% variability for different sampling frequency indicated on the vertical axis. Note that a frequency of one section in four gives a variation of FLN of less than 10% for areas with FLN higher than 3%. For weaker projections, a 1/1 frequency is required. *B*, Variation of SLN% (vertical axis) for areas with different FLN values (horizontal axis). Note that SLN is much less sensitive to sampling frequency and 1/4 gives stable values down to relatively weak projections. 1/1 is required for areas with an FLN value of less than 0.6. *C*, Relative contribution of auditory and STP cortex to inputs to area V1. By expressing the FLN of labeling in STP and auditory cortex with respect to the FLN of the STS movement complex (MT, MST, FST), we can show that the importance of these projections increases in the peripheral visual field (Falchier and others 2002).

ther than do the supragranular neurons. Therefore, to estimate the SLN of a projection zone, it is necessary to employ a high sampling frequency throughout the full extent of the projection zone. Exactly what sampling frequency is required is further complicated by the curvature of the cortex. The combined effects of the morphology of the projection zone and the cortical curvature are that reliable SLN values can only be obtained after counts of several thousand neurons per cortical area.

Operationally, obtaining stable SLN values requires charting neurons in a cortical area at regular intervals. This kind of investigation of cortical connectivity is also

interesting because it will also give information on the relative contribution of connections from each source area to the target area. We refer to this parameter as the FLN. The critical issue is, How high does the sampling frequency have to be to obtain stable values of FLN and SLN? This is an important question if we are to use SLN and FLN to obtain hierarchical distances and relative strength of input for cortical networks composed of numerous areas. To address this issue, we analyzed labeling in cortical areas following injection in the frontal eye field. The advantage of using the frontal eye field is that it receives input from up to 50 cortical areas.

We calculated the FLN and SLN using a frequency of 1/1 and compared this to the theoretical frequency derived from frequencies of 1/2, 1/4, and 1/8. The results are shown in Figure 3 *A,B*. What this analysis shows is that for both FLN and SLN, the minimum sampling frequency is highly dependent on the FLN values. Hence, setting the maximum acceptable error at 10%, a frequency of 1/2 is required to obtain reliable SLN values for areas with an FLN above 0.36%, and for lower FLN values, it is necessary to sample at 1/1.

Just how useful FLN can be in relating structure to function in the cortex is illustrated in a recent study that examined connectivity in area V1 in regions subserving different eccentricities of the visual field. Traditionally, cortical areas have been considered to show uniform physiological properties and therefore connectivity throughout. This was thought to be particularly well established in area V1 (Hubel and Wiesel 1974). To see if areal uniformity extended to cortico-cortical connectivity, we made injections of retrograde tracers at different eccentricities in area V1. This showed that as one moved from area V1 subserving the central visual field to the periphery, there was an eightfold increase in the FLN of area STP (Fig. 3C). Even more surprising was a hitherto unknown projection from the auditory cortex to area V1 subserving the peripheral representation of the visual field (Falchier and others 2002). The auditory input to peripheral V1 had an FLN comparable to that of the STS movement complex, which has a measurable and highly significant impact on the physiology of area V1 (Pascual-Leone and Walsh 2001). These results have several implications. First, they provide evidence of multimodal integration in early stages of the visual cortex of primates. Second, by showing that connectivity is measurably modified with eccentricity and in an area as intensively studied as area V1, they suggest that connectivity in higher order areas may also show important and as yet unsuspected peculiarities. This in itself suggests that there might be further and major changes in the organization of the visual cortex to be discovered. This is made more likely still by the fact that the SLN values of peripheral and central area V1 showed very important differences, suggesting that not only are different areas connected in central and peripheral representations, but their hierarchical relationships are radically different (Falchier and others 2000; Young and others 2000).

Computer analysis employing evolutionary optimization showed that the hierarchical analysis as implemented by Felleman and Van Essen cannot nail down the hierarchy of the primate cortical system (Hilgetag and others 1996). This is paradoxical because what this analysis also demonstrated is that the system is surprisingly strictly hierarchical (Hilgetag and others 1996). Optimization analysis pioneered by the Young group generates a topological model of cortical organization, which provides insights not available in the unidimensional models generated by hierarchical analysis (Young 1992). Topological models group areas that show similar

connectivity and separate areas with dissimilar connectivity. Because of their multidimensional character, the topological model can be expected to give important information on parallel pathways, which physiological studies have shown to be a prominent feature of the visual system. In fact, the topological model gave a clear indication of the dorsal and ventral streams and their convergence in area 46 (Young 1992). Interestingly, despite the fact that the topological model did not use information about laminar connectivity, both hierarchical and topological models were found to be significantly related, suggesting that both approaches will be required (Scannell and others 1995). Further embellishments on topographical analysis have been achieved by formulating the problem in terms of graph theory, which has provided an algorithm for dealing with the problem of missing data (Jouve and others 1998).

The hierarchical analysis of SLN data showed one intriguing departure from the Felleman and Van Essen model. In this model, the frontal eye field is located at a very high level of the hierarchy, whereas SLN analysis shows this prefrontal area to be at a much lower level and to have a feedforward projection to area V4 (Fig. 4) (Barone and others 2000). Although a caudal and long-distance connection is not expected to be feedforward in function, this finding fits with the physiological involvement of both the frontal eye field and area V4 in visual attention and, more important, the very short latencies to be found in the frontal eye field (Thompson and others 1996; Reynolds and Desimone 2003). In fact, the idea that the frontal eye field is centrally placed in the cortical network had been suggested in the topological study of Jouve who proposed it could constitute a relay area between dorsal and ventral streams (Jouve and others 1998). To further investigate this issue, we have implemented a topological analysis using the algorithm of Jouve and including the recently discovered additional connections (Barone and others 2000) (Fig. 4). This confirms the central location of the frontal eye field. In the Felleman and Van Essen hierarchical analysis, and in both the topological models of Jouve and Young, area V1 is located eccentric to the cortical network. In the update of Jouve's model in Figure 4, area V1 is located within the cortical network. This finding is compatible with recent theories suggesting that area V1 fulfills higher functions (Hochstein and Ahissar 2002; Pins and Ffytche 2003; Ress and Heeger 2003; Super and others 2003).

Perspectives

The complementary power of hierarchical and topological analysis needs to be harnessed in a single procedure. This can be achieved by 1) implementing a topological analysis in which connections are weighted according to their SLN and FLN values and 2) updating our connectivity database by distinguishing connections in cortex subserving central and peripheral visual fields. Preliminary findings suggest that this will provide novel

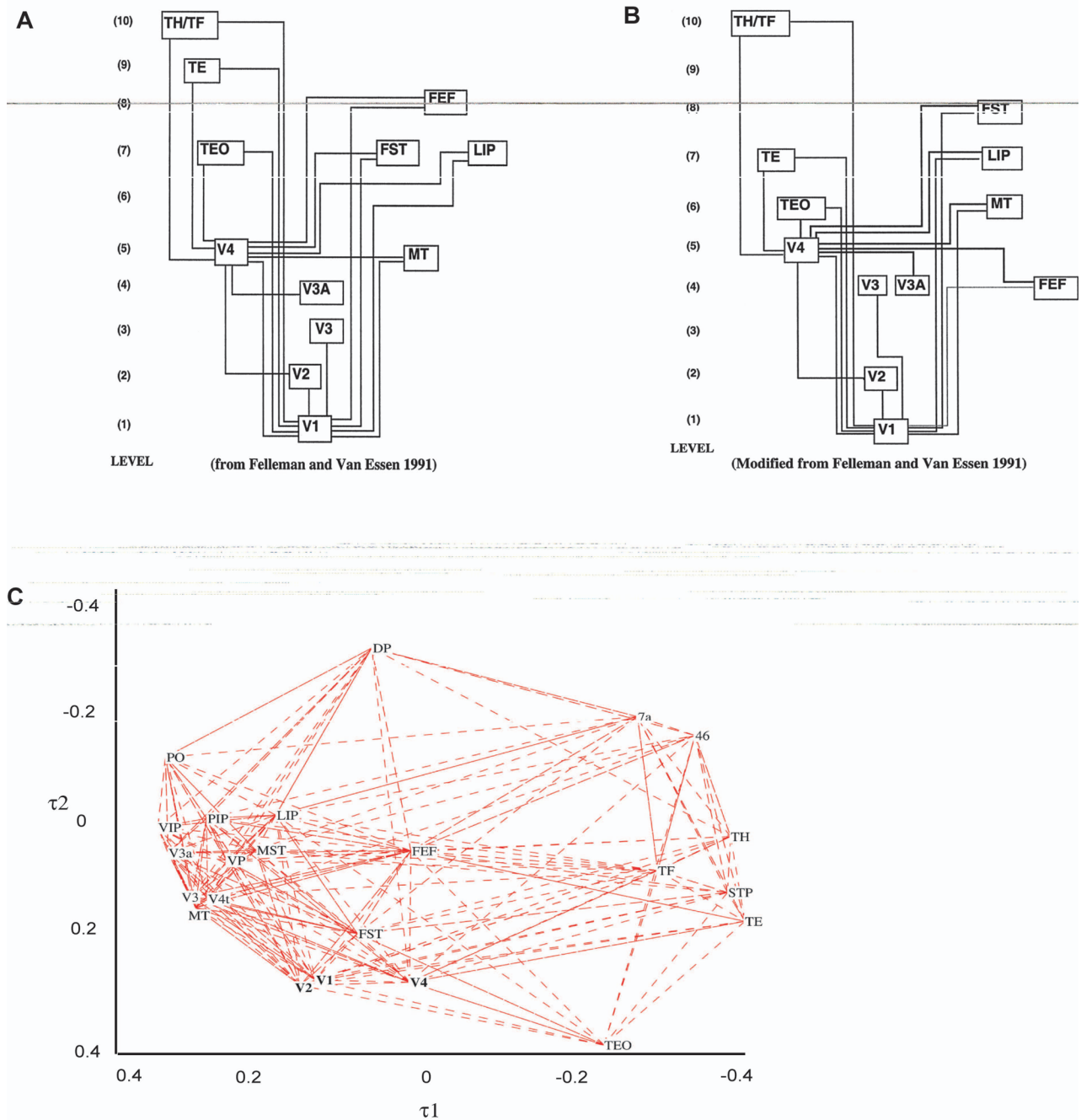


Fig. 4. Hierarchical model of relations of the frontal eye field and V4. *A, B*, Comparison of the hierarchical model of the primate visual system constructed from Felleman and Van Essen (*A*) and using SLN (*B*) (Barone and others 2000). *C*, Topological model of cortex using Jouve's algorithm (Jouve and others 1998) on an updated database taken from Barone and others (2000).

insight into the functional architecture of the cortical network. Such a procedure will be an important step toward integrating anatomical and functional models of cortical architecture (Kotter and Sommer 2000; Petroni and others 2001).

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