The primate connectome in context: Principles of connections of the cortical visual system

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ABSTRACT

Which principles determine the organization of the intricate network formed by nerve fibers that link the primate cerebral cortex? We addressed this issue for the connections of primate visual cortices by systematically analyzing how the existence or absence of connections, their density as well as laminar patterns of projection origins and terminations are correlated with distance, similarity in cortical type as well as neuronal density or the thickness of cortical areas. Analyses were based on four extensive compilations of qualitative as well as quantitative data for connections of the primate visual cortical system in macaque monkeys (Felleman and Van Essen 1991; Barbas 1986; Barbas and Rempel-Clower 1997; Barone et al. 2000; Markov et al. 2014). Distance and thickness similarity were not consistently correlated with connection features, but similarity of cortical type, determined by qualitative features of laminar differentiation, or measured quantitatively as the areas' overall neuronal density, was a reliable predictor for the existence of connections between areas. Cortical type similarity was also consistently and closely correlated with characteristic laminar connection profiles: structurally dissimilar areas had origin and termination patterns that were biased to the upper or deep cortical layers, while similar areas showed more bilaminar origins and terminations. These results suggest that patterns of corticocortical connections of primate visual cortices are closely linked to the stratified architecture of the cerebral cortex. In particular, the regularity of laminar projection origins and terminations arises from the structural differences between cortical areas. The observed integration of projections with the intrinsic cortical architecture provides a structural basis for advanced theories of cortical organization and function.

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1. Introduction

Macroscopic connections among cortical areas form intricate networks for neural communication (Van Essen et al., 2013). These networks are neither completely nor randomly wired, and their organization has been the subject of extensive investigations (reviewed in Sporns et al., 2004; Bullmore and Sporns, 2009; Sporns, 2010).

An essential question is what determines the existence or absence of connections, since not all possible connections exist. A starting point is the observation that neighboring areas or neighbors-one-over are frequently connected (Barbas and Pandya, 1989), accounting for about half of the connections in primate visual cortex (Young, 1992). While proximity may contribute to the formation of connections (Ercsey-Ravasz et al., 2013), it cannot be the only factor, because some connections extend across considerable distances (e.g., Barbas and Mesulam, 1981; Kaiser and Hilgetag, 2006; Markov et al., 2013). Another model suggests that connections are formed between areas of similar thickness

(He et al., 2007; Bassett et al., 2008; He et al., 2008; Liu et al., 2008; Bassett and Bullmore, 2009; He et al., 2009). Alternatively, a structural model posits that similarities in overall laminar organization (Barbas, 1986; Barbas and Rempel-Clower, 1997; Medalla and Barbas, 2006) help explain the presence and patterns of connections (Barbas and Rempel-Clower, 1997; Barbas et al., 2005a).

An important feature of connections is their strength – the number of neurons in a pathway – that may help estimate functional impact (Vanduffel et al., 1997). Strength varies considerably across pathways (MacNeil et al., 1997; Scannell et al., 2000; Hilgetag and Grant, 2000) and possesses a logarithmic (Scannell et al., 2000) or lognormal (Markov et al., 2011) global distribution, where a few pathways are very dense and most others are either sparse or absent. The factors that underlie this distribution are still incompletely understood (Kaiser et al., 2009).

A further question concerns the laminar patterns of connections, reviewed in Felleman and Van Essen (1991), which emanate and terminate in functionally distinct laminar micro-environments (Barbas et al., 2005b). Laminar patterns of connections are diverse but strikingly repetitive. For example, in the cortical visual system, connections can be arranged into sequences or hierarchies. In such sequences, projections

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that mostly originate from upper cortical layers and terminate in the middle-to-deep layers ('feedforward') point in one direction, while the reciprocal ('feedback') projections that mostly originate from deep layers and terminate in upper cortical layers point in the opposite direction of the sequence. Most visual projections fit such a scheme, with only 6 violations out of 318 patterns (Hilgetag et al., 1996). By contrast, if such arrangements are attempted for randomly assigned projection patterns, a large number of disagreements (>100) remain (Hilgetag et al., 2000b). Thus, laminar projection patterns demonstrate a remarkably regular motif in cortical organization. It has been suggested that the regularity depends on cortical structure (Barbas, 1986; Barbas and Rempel-Clower, 1997), physical distance (Bullier and Nowak, 1995), or hierarchical rank (Barone et al., 2000).

Here we systematically investigated factors that contribute to the organization of cortical connections, by quantitative hypothesis testing based on distinct proposed models. To test these models, we studied extensive data from various sources to increase the reliability and generality of the findings: a collation of qualitatively described primate visual connections (Felleman and Van Essen, 1991); quantitative datasets from the laboratory of Kennedy (Barone et al., 2000; Markov et al., 2014); and newly compiled quantitative data on connections and cortical structure from our laboratory (Barbas, 1986; Barbas and Rempel-Clower, 1997). The primate visual cortical system is ideal for this study, because extensive available data make it possible to test to what extent alternative models, based on differences in distance, cortical thickness, or cortical structure between connected areas, best account for the existence, absence, density and laminar distribution of connections. Preliminary results from this study were presented in abstract form (Hilgetag et al., 2008).

2. Methods

2.1. Connection datasets

We analyzed the following four datasets which provide qualitative and quantitative information on the existence or absence, strength, as well as laminar patterns of projection neurons in the primate visual cortex in macaque monkeys. These data include the landmark compilation of Felleman and Van Essen of visual connections (Felleman and Van Essen, 1991), two sets of quantitative laminar projection patterns for visual projections (Barone et al., 2000; Markov et al., 2014), as well as a partly independent set of prefrontal afferent neurons originating in visual cortex. The latter data have been recompiled from published studies of our laboratory (Barbas, 1986, 1993; Barbas and Rempel-Clower, 1997) and are comprehensively presented in the present paper for the first time. Essential features of the analyzed datasets are summarized in Table 1. We used statistical approaches, such as rank correlations, that are appropriate for the respective data scales. Probabilities of the

Table 1
Essential features of the analyzed datasets.

Dataset	Analyzed feature	Data scale
Global visual connections (Felleman and Van Essen, 1991)	Existence/absence of projections	Qualitative (nominal)
	Laminar projection origins and terminations	Qualitative (ordinal)
Visual prefrontal afferents (Barbas, 1986, 1993; Barbas and Rempel-Clower, 1997; Table 2)	Existence/absence and strength of projections	Qualitative (nominal), quantitative (ratio)
	Laminar projection origins	Quantitative (ratio)
V1 and V4 afferents (Barone et al., 2000)	Laminar projection origins	Quantitative (ratio)
Global visual afferents (Markov et al., 2014)	Laminar projection origins	Quantitative (ratio)

findings are reported at levels p > 0.05, p < 0.05, and p < 0.001, and findings were considered significant if p < 0.05.

2.1.1. Dataset 1: 'Global visual connections'

The dataset derives from Felleman and Van Essen's compilation of qualitative information on the existence and absence as well as laminar patterns of connections among areas of the primate cortical visual system (Felleman and Van Essen, 1991). For all analyses reported here, areas MIP and MDP were excluded due to limited information about their connections. Moreover, subdivisions of areas PIT (PITd, PITv), CIT (CITd, CITv), AIT (ATId, AITv) and STP (STPp, STPa) were considered separately, and information that was available for a whole area (such as PIT) was assigned to both subdivisions. This treatment led to a set of 30 areas, as in previous studies (e.g., Hilgetag et al., 2000a,b). For a list of area name abbreviations, see Felleman and Van Essen (1991).

First, the dataset provided information on the existence or absence of pathways among the 30 areas (based on Felleman and Van Essen, 1991, their Table 3). Specifically, it distinguished between connections that were explicitly tested and found either existing (N = 315) or absent (N = 323) as well as pathways that were reported as untested (N = 232).

Second, the dataset included qualitative information on patterns of laminar origin and laminar termination of pathways (Felleman and Van Essen, 1991, their Table 5). In the present analysis, we used the following five laminar origin patterns as listed by Felleman and Van Essen: 'supragranular' (S), 'bilaminar' (B), 'infragranular' (I), and the combinations S/B and B/I; as well as these five termination patterns: 'layer 4 predominant' (F), 'columnar' (C), 'multilayer avoiding layer 4' (M), and the combination patterns F/C and C/M. Patterns listed as M(s) or M(i) were grouped with the M pattern. Three projections that were assigned contradictory termination patterns listed as F/M (suggesting that terminations were simultaneously predominating in layer 4 as well as avoiding layer 4) were ignored for the present analysis. Altogether, there were 224 origin patterns included in the present analysis ($N_S = 71$, $N_B = 74$, $N_I = 37$, $N_{S/B} = 27$, $N_{B/I} = 15$) and 144 termination patterns ($N_F = 49$, $N_C = 14$, $N_M = 58$, $N_{F/C} = 10$, $N_{C/M} = 13$).

Finally, the Felleman and Van Essen dataset also provided information on the general orientation of connections among visual areas (Felleman and Van Essen, 1991, their Table 7), which were derived from an interpretation of the origin and termination patterns in Felleman and Van Essen (1991, their Table 5). The link between two areas was called 'feedforward' (FF), if the projection had a 'supragranular' origin in the source area, or a 'supragranular' or 'bilaminar' origin in the source area and a 'predominantly layer 4' termination in the target area. The link was called 'feedback' (FB), if the origin in the source area was 'infragranular', or 'infragranular' or 'bilaminar' and the termination in the target area avoided layer 4. Finally, the connection was called 'lateral' (L), if it had a 'bilaminar' origin in the source area and a 'columnar' termination in the target area. From these rules it is clear that connections with bilaminar origins could not be classified in the absence of termination information. The classification rules are summarized in Felleman and Van Essen (1991, their Fig. 3). The resulting five connection types were 'feedforward' (FF; $N_{FF} = 131$), 'feedback' (FB; $N_{FB} = 129$), 'lateral' (L; $N_L = 10$), as well as the intermediate patterns 'feedforward or lateral' (FF/L; $N_{FF/L} = 24$) and 'lateral or feedback' (L/FB; $N_{L/FB} = 24$), producing a total of 318 classified connections.

Felleman and Van Essen (1991) indicated that some constraints may be less reliable when the information had been published in conference abstracts. In the present analysis such constraints were not specifically distinguished.

2.1.2. Dataset 2: 'Visual prefrontal afferents'

We also analyzed a database of prefrontal afferent projections compiled from data produced in the Barbas laboratory. These projection neurons originate in visual, visuomotor, or polymodal association and limbic cortices; the latter two lie next to high-order visual association cortices and are connected with them. The compilation includes