Connectivity in the visual system; evidence from modeling, fMRI and DTI = Connectiviteit in het visuele systeem : bewijs op basis van modeleren, fMRI en DTI

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Connectivity in the visual system

Evidence from modeling, fMRI and DTI

Cover: based on a drawing 'ingewikkeld' made in 1991

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Connectiviteit in het visuele systeem

Bewijs op basis van modeleren, fMRI en DTI

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht, op
gezag van de Rector Magnificus, Prof. Mr. G. P. M. F. Mols volgens het
besluit van het College van Decanen, in het openbaar te verdedigen op
vrijdag 9 mei 2008 om 14.00 uur

door

Michael Capalbo

Geboren op 11 februari 1977 te Eindhoven

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Prof. Dr. Jaap Murre (Universiteit van Amsterdam)

Prof. Dr. P. de Weerd

Dr. E. Formisano

Waarom schrijf ik

Ik schrijf omdat ik wil schrijven
dat ik gelukkig ben.

Op een dag zal het zover zijn
en zal ik schrijven –
met mijn tong tussen het puntje van mijn tanden,
en met rode oren en rode wangen:
ik ben gelukkig.

Als ik daarna ooit nog twijfel
en meen dat ik verdrietig ben of de wanhoop nabij
of zelfs reddeloos verloren,
kan ik altijd opzoeken wat ik werkelijk ben:
gelukkig

Toon Tellegen – Gewone gedichten (1998)

Voor mijn moeder

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Chapter 1

General Introduction

It took a long time for man to realize that the brain was the organ that coordinates and controls behavior. The Egyptians preserved liver, lung, stomach and intestines in their tombs if they could afford it, but discarded their brains as unimportant. The Greek thinker Aristotle thought the heart was the most important organ and that the brain was merely providing the cooling for our heart. It was not until the nineteenth and twentieth centuries, when Paul Broca proved that localized parts of the brain had specific functions and Ramón y Cajal revealed that the brain had a cellular structure, that scientists accepted the brain as the organ that allows us to perceive and interact with the world. (e.g. see Finger, 2000)

One of the first questions that was raised about the brain, once its true importance for perception was realized, was about the organization of the visual system. We define the *visual system* as that part of the brain that is involved in visual perception, and *visual perception* as the process of acquiring knowledge about environmental objects and events by extracting information from the light they emit or reflect (Palmer, 1999).

We often take our own visual perception for granted, because all we need to do is open our eyes and look. Nevertheless, visual perception is very important to us, something we can easily come to realize if we imagine ourselves blind. Despite the fact that it comes very natural to us, the neural mechanisms underlying visual perception turn out to be enormously complex. Neuroscientific investigations revealed parts of the neural machinery that explain how we perceive color (Bartels *et al.*, 2000; Lueck *et al.*, 1989), how we recognize human faces (Kanwisher *et al.*, 1997; Perrett *et al.*, 1982) and how visually impaired patients can ‘see’ without being aware of what they see (Goebel *et al.*, 2001; Weiskrantz *et al.*, 1974). The neuroscientific study of the visual system was not only successful because of its enormous relevance for our everyday life, but probably also because there is such a long tradition of research in the domain of visual perception. In the 19th and 20th century the Structuralists and the Gestaltists already contributed considerably to our understanding of visual perception (Palmer, 1999). They created a foundation of knowledge on visual perception that was combined with neuroscientific research into the visual system. When this field was infused with technological innovations like electrophysiological recording and in-vivo imaging techniques a successful new field was born: the study of visual perception in the field of cognitive neuroscience.

In this thesis we aim to contribute to this research tradition on the visual system. Our aim is to study *the large-scale structure of the visual system*, i.e., the overall structure of the visual system at the level of functionally defined areas and their interconnections.

Problems and Paradoxes

There are still some contradictions within our knowledge of the large-scale structure of the visual system and a lot of open questions. Below we will try to describe some of the contradictions we aim to solve and some open questions we will try to answer in this thesis.

Limitations of existing large-scale models

The large-scale models of the visual system that have been proposed to date (most notably the hierarchical model by Felleman and Van Essen, 1991) suffer from a number of limitations. In this thesis we will try to deal with the following four limitations. (1) The topology of most models depends heavily on the method used during data collection, whereas they should be similar as they describe the same physical system. (2) Most models do not have enough constraints to determine the topology of the model. This means that different topologies are possible using the same data. (3) Most models are incomplete, meaning that data is not available on all parts of the model (4) Most models are restricted, because they only include a number of areas, leaving out other areas which might be vital to explain certain functions of the visual system. (Mountcastle, 1998)

Simultaneous latencies

The location of a certain area in the large-scale structure of the visual system can be characterized in several ways. One possible method to characterize this location is to count the number of other areas between itself and where the source of the visual signal in the brain, the eyes. This method does not so much describe the absolute distance from the eyes, but if we assume that processing takes place in each area, this method describes the amount of processing needed before a certain visual signal reaches a certain area. Therefore this ‘processing distance’ should be related to the amount of time it takes for the visual signal to first reach an area. However, several authors have noted that areas that have a very different place in the visual system have almost identical latencies (Bair, 1999; Nowak *et al.*, 1998; Schmolesky *et al.*, 1998).

Human lesion studies

Some remarkable findings have emerged from research into brain-damaged human individuals. In these individuals, large parts of the primary visual cortex have been badly damaged on one side of the brain. Although we would expect areas that supposedly get their input from the damaged part of the brain to be heavily impaired, in fact the activity in these higher visual areas is close to the normal activity on the undamaged side of the brain (Goebel *et al.*, 2001; Schoenfeld *et al.*, 2002).

Research aims

The main aim of this thesis is to map the large-scale structure of the primate visual system. While doing so we will attempt to tackle the three problems mentioned above. Not only do we want to improve the previous models, but we also aim to formulate a model of our own that might explain the apparent paradoxical findings in monkeys and humans. To achieve this we aim to use convergent evidence (Baars, 2007; Gazzaniga *et al.*, 1998) from multiple species and with different methods. In the long run gaining more knowledge on the large-scale structure of the visual system might help to improve our understanding of the neural causes of visual impairments and how we can help patients suffering from these impairments.

Below we will describe the methods at our disposal and the structure and function of some of the more important parts of the visual system. Our description is confined to the methods and parts of the visual system that are of relevance to our investigations.

The methods

Neuroscience, cognitive neuroscience, and computational neuroscience are all partly defined by the methods they employ. Neuroscience took flight when methods became available to study neural tissue, cognitive neuroscience was boosted by the invention of in vivo imaging techniques like functional Magnetic Resonance Imaging (fMRI). Computational neuroscience evolved when the knowledge gained from the two previously mentioned fields was integrated with computer science. The research questions in this thesis are addressed using methods - or the data obtained from methods - from all three fields.

Neuro-anatomical tract tracing methods

The most obvious way to study connectivity in the brain is to study how neurons or groups of neurons are connected. Tract tracing methods or tracers for short employ stains that allow neuroanatomists to study this. Stains are chemical substances that are selectively absorbed by specific components of a neuron. Tracers are a certain class of stains that are transported through neurons as to reveal an entire neural tract allowing the identification of physical connections between areas in the brain. There are two main types of tracers: retrograde and anterograde tracers. Retrograde tracers (e.g. Horseradish Peroxidase, see Mesalun, 1982) are injected at the target and stain the tract down to the source, while it is the other way around for anterograde tracers (e.g. PHA-L, see Cucchiari *et al.*, 1990). Tract tracing methods can only be used in animals as it requires in vivo injection and subsequent post-mortem analysis in prepared brain slices. (Kobbert *et al.*, 2000)

Database collations of tract tracing results

The results from tract tracing methods have cumulated over the years in hundreds of publications from a wide range of labs. The integration of the results of all those tract tracing studies requires the tools and algorithms of computer science. Database methodologies allow for the representation of all the tract tracing data in an objective, coordinate-free, parcellation-based fashion and for the integration of contradictory data. The publicly available Cocomac database applies such a methodology and can be queried through the online interface CoCoMac-Online at <http://www.cocomac.org/>. (Kotter, 2004). With a mathematical method called Objective Relational Transformation (ORT), it is possible to combine tract tracing data from any parcellation scheme to achieve a further integration (K. E. Stephan *et al.*, 2000). In chapter 2 we will use the Cocomac database and ORT to summarize a large amount of tract tracing data in a connectivity matrix.

Microelectrode recordings of single cells to record latencies

Microelectrode recording is inserting a very thin electrode into an animal's brain to measure electrical changes in the brain-cells around it. Unlike fMRI, microelectrode recording is a direct measure of brain activity. Microelectrode recordings from the brain of primates performing various behaviors can reveal the neuronal activity that carries information about various cognitive functions. (Evarts, 1968; Hubel, 1957; Hubel *et al.*, 1962) In latency studies, microelectrode recording is used to determine the time it takes for neural signals to traverse from one brain area to the next one. To measure such latencies, an animal is anaesthetized and (multiple) electrodes are inserted into the animal's brain to measure the onset latencies of single cells to visual stimuli. Despite the fact that the animal is anaesthetized, visual stimuli evoke neural activity in the visual areas. The latency is defined as the time it takes for the first spike to reach one of the electrodes. (e.g. see Schmolesky *et al.*, 1998) In chapter 2 we will use published latency data to constrain our connectivity-matrix model of the visual system.

MRI and fMRI

Magnetic Resonance Imaging (MRI) and functional Magnetic Resonance Imaging (fMRI) are closely related non-invasive imaging methods. Both methods provide the possibility to obtain images of the brain in living, awake subjects. To acquire MRI images subjects are positioned in a so-called Magnetic Resonance scanner (MR-scanner) which generates a strong static magnetic field (3 Tesla in the work presented here, roughly 60,000 times the strength of the earth magnetic field). Brain tissue contains water which in turn contains hydrogen protons. The hydrogen protons behave like miniature magnetic dipoles when placed in a magnetic field and can be manipulated by radiofrequency (RF) pulses emitted by the scanner. Switching the RF pulses on and off pushes protons into the excited and resting state, respectively. When returning to the resting state, the protons

emit small RF pulses. The summed strength of these pulses is proportional to the number of excited protons and therefore an effective measure of the amount of water in different kinds of brain tissue. This allows us to make three-dimensional images of brain tissue otherwise known as ‘structural images’ of the brain. (Bandettini et al., 2000; Matthews, 2001)

Functional Magnetic Resonance Imaging provides an *indirect* measure of neural activity in the brain because it measures the blood-oxygen level in the brain rather than the brain activity itself. Although the fMRI signal originates from a different source (blood oxygen) than that of MRI (hydrogen protons) their underlying principles are very similar. Oxygenated and de-oxygenated blood differ in their magnetic susceptibility and therefore vary in the amount of RF signal they emit when probed; oxygenated blood contains more diamagnetic oxyhemoglobin and therefore increases the signal compared to de-oxygenated blood. Because neural activity leads to a localized increase in oxygenated blood, this leads to an increased RF signal from the surrounding brain tissue. Therefore this signal is called the ‘Blood Oxygenation Level Dependent’-signal or BOLD-signal. (Bandettini et al., 2000; Matthews, 2001)

Registration of the structural MRI and the functional fMRI data offers the possibility of visualizing exactly what part of the brain is responsible for what function. In this way, the functional specialization of the brain can be mapped yielding information on the functional modularization of the brain. In chapter 3 we will use MRI and fMRI to map the large-scale structure of the functional modules of the human visual system.

DTI and fiber-tracktography

MRI and fMRI allow us to reveal the functional modules of the brain but do not provide information on how the modules are interconnected. Using the MR-scanner three kinds of connectivity can be ascertained: functional, effective and structural connectivity. Functional connectivity is defined as the temporal correlation between remote neurophysiological events. Effective connectivity is defined as the influence exerted from one neural population on another (Friston et al., 1994). Both functional and effective connectivity are indirect measures of connectivity. Structural or anatomical connectivity refers to the physical axonal connection between anatomical brain structures. Because this is a direct measure of connectivity, structural connectivity is the preferred connectivity measure in this thesis. Structural connectivity is traditionally studied with tract tracing methods (see above) or post-mortem dissection. Unfortunately, both techniques are not suitable for determining axonal connectivity in humans (Behrens *et al.*, 2003; Kim *et al.*, 2006).

Fortunately, recently two closely related alternative techniques were invented that *are* suitable to humans: diffusion weighted magnetic resonance imaging and diffusion tensor imaging (DTI). With DTI the structural connectivity of the brain can be studied non-invasively in humans, albeit indirectly. DTI exploits the diffusion properties of water molecules in the brain. The diffusion of water molecules enclosed by neural fibers follows the direction of the fibers. DTI measures the directional gradient of water diffusion in the brain with an MRI-scanner to visualize the fiber bundles in the human brain. By applying a line propagation algorithm to the raw DTI data, large white-matter fiber-bundles can be reliably traced from area to area (e.g. Le Bihan, 2003; Le Bihan et al., 2001).

In chapter 4 we will use DTI to look at the structural connectivity in the human visual system.

The structure and function of the elements of the visual system

As we mentioned earlier, a great deal is already known about visual perception and the visual system. In the last few decades a number of distinct, anatomically or functionally defined areas that are involved in visual perception have been described. While the exact location, extent and function of these areas remain debated, we will shortly describe the areas that are generally agreed upon by neurocognitive scientists and that are used in this thesis. Note that the name given to an area or even the parcellation of areas may differ between species and publications. In chapter 3 we map the locations of most of these areas in the human subjects. The general lay-out however, is straightforward to describe: the retinas in the eyes generate the neural signal, which is propagated along the optic nerve, the optic nerves crosses at the optic chiasm and then the neural signal reaches the *sub-cortical nuclei*, before going on to the visual cortex (See figure 1).

Figure 1: A schematic view of the structures involved in the early stages of visual processing (illustration reproduced from Kalat, 1995)

The visual cortex can be divided into *early and higher visual areas*. The early visual areas can be described as the areas that are activated relatively early during visual processing. The higher visual areas are supposedly involved in ‘higher order’, more complex, processing in the visual system. Because there is no consensus on the exact criteria necessary to differentiate between early and higher visual areas, will define them operationally; the early visual areas are the areas that can be localized with an fMRI analysis technique called retinotopic mapping, the higher visual areas those areas that can be delineated with ‘conventional’ fMRI localizers. Below we will briefly describe the subcortical nuclei, early visual areas and higher visual areas that are important in this thesis.

Sub-cortical nuclei

The sub-cortical nuclei are found below the cortex and these nuclei are often seen as ‘relay stations’ between the eye and the brain. The most important nuclei in this thesis are the Lateral Geniculate Nucleus, the Superior Colliculus and the Pulvinar. The *Lateral Geniculate Nucleus* or *LGN* is the key gateway to visual signals entering the cortex. No significant transformation of the neural signal occurs in the LGN. However the LGN is more than just a gateway, as it is probably involved in regulating the flow and strength of the visual signal to the cortex, possibly modulated by massive cortical feedback from V1 (e.g. Casagrande *et al.*, 2002). Like the LGN, the *Superior Colliculus* is also connected to the retina. It is involved in the rapid spontaneous movements of the eyes, the so-called saccadic movements. More specifically, it is responsible for the signaling of upcoming gaze locations and is likely to be involved in the control of eye-movement and orientation (Wurtz *et al.*, 1980). The *Pulvinar* is also connected to the retina and is known to be reciprocally connected to large parts of the brain. It is involved in signaling what part of a visual scene is ‘salient’ and requires attention, but is probably also involved in signaling saliency in other modalities (Grieve *et al.*, 2000). In this thesis we shall also refer to the sub-cortical *nuclei* as sub-cortical *areas*. In this thesis we shall argue that the connections from the subcortical nuclei to the cortex play a more important role than is often assumed in the literature.

Early visual areas

All areas considered to be early visual areas in this thesis, namely V1, V2, V3, V3A, VP and V4v, have a retinotopic organization, meaning that they are organized in a map-like manner, with neighboring locations in the visual field projecting onto nearby locations in the brain. The primary visual cortex or area *V1* is the area in the brain where most of the connections from the LGN go to. The primary visual cortex is generally assumed to extract elementary spatiotemporal features, such as, orientated edges, color, and direction of motion, from the ‘raw’

visual input. The second visual area or *V2* surrounds *V1* and has many reciprocal connections with it. *V2* contains neurons that respond to both real and illusory contours and therefore might be involved in separating a figure from its ground. (Koch, 2004b; von der Heydt *et al.*, 1984). Directly adjacent to *V2* is the area *V3* that might have a role in the processing of global motion (Braddick *et al.*, 2001). *V3* can be subdivided into a dorsal and ventral part. Adjacent to dorsal *V3* is *V3A*. Ventral *V3* is often referred to as *VP*. The next stage in the cortical hierarchy is area *V4*. This area can be subdivided into four parts (left and right dorsal *V4* and left and right *V4v*) and is involved in color processing subserving color constancy (McKeefry *et al.*, 1997). Because we use operational criteria to differentiate between early and higher visual areas (see above) we have classified *V4v* as an early visual area and *V4* as a higher visual area.

Higher visual areas

The higher visual areas described here, *V4*, *MT*, *MST*, *FEF*, *LOC*, *FFA* and *PPA*, are involved in more complex and abstract processing than the early visual areas. Area *MT* (Middle Temporal), sometimes referred to as area *V5*, contains neurons that are highly reactive to motion and this area is therefore often thought to measure or detect motion. However, recent work has revealed that a more accurate description of the function of *MT* is that it integrates and segments visual scenes (Born *et al.*, 2005). Area *MST* (Medial Superior Temporal) is also motion sensitive but in a different manner as it seems to be involved in detecting self-motion direction from clues in the background, while compensating for eye-movement (Britten *et al.*, 2002). Area *FEF* (Frontal Eye Fields) is also related to motion albeit in a totally different manner. Like the *SC* it is also involved in eye movement, but unlike the *SC* it really steers the eye during both rapid spontaneous eye movements (saccades) and smooth pursuit eye movement (Petit *et al.*, 1997).

There are also a number of areas in the visual cortex that are responsible for recognizing certain categories of objects or scenes. The Lateral Occipital Complex, or area *LOC* (sometimes abbreviated *LO*) responds very strongly to objects in general and this activity is independent of the familiarity of the objects, from which we infer that *LOC* is responsible for the recognition of objects without any semantic or cognitive processing (Malach *et al.*, 1995). Area *FFA* (the Fusiform Face Area) is specialized in the perception of faces (Kanwisher *et al.*, 1997). The area *PPA* or Parahippocampal Place Area is not, as the name suggests, selectively involved in the perception of places, but is very likely involved in encoding new perceptual information about the appearance and layout of scenes (Epstein *et al.*, 1999).

The primate visual system

The human and the monkey visual system are very similar because of the relatively small evolutionary distance between the species, allowing us to investigate the neural basis of the visual system in monkeys with invasive techniques. Although both visual systems are far from identical, areas differ greatly in location and extent, all areas discussed here can be found in both the human and monkey visual areas, except LOC FFA and PPA (Tootell *et al.*, 2003). Even for these last three human areas, monkey homologies have been suggested.

Research goals addressed in the following chapters

In *Chapter 2* the goal is to find topologies of the large-scale structure of the visual system that fit both the available latency data as the connectivity data as summarized in the Cocomac database. The idea is to combine both kinds of data in a data driven optimization method so that the optimal topology might emerge from the data. The topologies that emerge thus might give us an idea on what is necessary to improve upon current models of the visual system.

The goal of *Chapter 3* is to investigate the large-scale structure of the human visual system. By localizing a large amount of areas that are part of the visual system with fMRI we shall attempt to map the large-scale functional architecture of the visual system. Unlike previous work, we focus not only on mapping cortical, but also on sub-cortical areas. The resulting maps serve as a good starting point for structural, functional or effective connectivity analyses.

The goal of *Chapter 4* is to investigate the possible structural connections between the subcortical areas and all other areas in the human visual system with DTI, using the functional map from chapter 3 as a starting point. As we argue in chapter 2, the connections from the sub-cortical nuclei to the cortex that turn out to be important in explaining the simultaneous latencies in monkeys could also explain the results in the human lesion studies.

In *Chapter 5* the findings of the studies reported in chapter 2-4 and their implications for the large-scale connectivity of the visual system are discussed. We will also discuss if the goals of this thesis have been met. The results obtained from different species and with different methods will be integrated to try and specify a model for the large scale structure of the primate visual system.

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Chapter 2

Modeling the Structure of the Visual System Using Structural Connectivity and Response Latencies

This chapter is based on:

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Abstract

Several approaches exist to ascertain the connectivity of the brain and these approaches lead to markedly different topologies, often incompatible with each other. Specifically, recent single-cell recording results seem incompatible with current structural connectivity models. We present a novel method that combines anatomical and temporal constraints to generate biologically plausible connectivity patterns of the visual system of the macaque monkey. Our method takes structural connectivity data from the CoCoMac-database and recent single-cell recording data as input and employs an optimization technique to arrive at a new connectivity pattern of the visual system that is in agreement with both types of experimental data. The new connectivity pattern yields a revised model that has fewer levels than current models. In addition, it introduces subcortical-cortical connections. We show that these connections are essential for explaining latency data, are consistent with our current knowledge of the structural connectivity of the visual system, and might explain recent functional imaging results in humans. Furthermore we show that the revised model is not under-constrained like previous models and can be extended to include newer data and other kinds of data. We conclude that the revised model of the connectivity of the visual system reflects current knowledge on the structure and function of the visual system and addresses some of the limitations of previous models.

Introduction

What are the elements of the visual system in the brain and how are they connected? A large amount of research in vision science has been devoted to these questions. The most apparent way to answer the question of connectivity is to look at the structural connections between functionally defined areas in the visual system, and these have been studied systematically with experimental tracing studies in rats, cats and monkeys. Because of the invasive and time-consuming manner in which these studies have to be done, results are gathered incrementally and scattered across hundreds of separate research publications. If all these separate results are put together, a model of the large-scale structural connectivity of the visual system can be made. For such a model to make sense however, it should be structured according to an organizational principle. Because there are several possible organizational principles, a number of different models can be found in the literature (see e.g. Andersen *et al.*, 1990; Distler *et al.*, 1993; Felleman and Van Essen, 1991; Zeki *et al.*, 1988). However, the model published by Felleman and Van Essen in 1991 has since been accepted as a standard model, and is cited in numerous academic books (e.g. see Koch, 2004c) and articles (e.g. see Bourne *et al.*, 2006). These models can be compared in figure 1.

Figure 1: Schematized models of the visual system compared. Areas are placed in a level according to the figures in the original publications. If levels were not present in the original model, areas were placed according to hodology (Nicollelis *et al.*, 1990), i.e. according to the shortest possible route to connect two areas. The original model by Felleman & Van Essen contains many more levels and areas in the original (see figure 2).

However, a number of limitations of all these models have been identified. We will focus on five limitations, namely that most models are (1) method dependent (2) indeterminate, (3) incomplete, (4) restricted, and (5) invalid with respect to latency data. We discuss each of these limitations in more detail below. (1) *The structure of the models is dependent on the method used.* All three models mentioned earlier are based on studies using different methods. The hierarchical model (Felleman and Van Essen, 1991) is based on the pattern of origin and

termination of fibers to and from an area, the models by Andersen Asanuma *et al* (1990) and the model by Distler *et al* (Distler *et al.*, 1993) are based mostly on tract tracing data and the model by Zeki and Shipp (1988) is used to explain segregation and integration of features of the visual image. If we look at figure 1 we see that all these models differ, yet they all describe the same system. It seems that the structure of these large-scale models is very much dependent on the kind of data used to constrain the model and the phenomena it is designed to explain, whereas these models should agree as they describe the same physical system. (2) *The models are indeterminate.* Hilgetag, O'Neill *et al.* (1996) developed an algorithm to generate 150,000 candidate hierarchies, all of which agree with the anatomical constraints specified by Felleman & Van Essen (1991) in their hierarchical model. Every one of these hierarchies violated fewer constraints than the original Felleman and Van Essen hierarchy. In addition, only two of the considered 30 brain areas were assigned to levels consistently across these candidate hierarchies. From these results, Hilgetag *et al.* concluded that the constraints (connection types) used by Felleman & Van Essen reduce the number of candidate hierarchies insufficiently. In other words, the hierarchical model, and probably all models like it are under-constrained. (3) *The models are incomplete.* The connectivity data employed by most of the models of the visual system are incomplete because their connection matrix contains many unknown entries (Mountcastle, 1998). A large number of possible connections have not been investigated. Even with the additional studies done since then, a large percentage remains unknown. (4) *The models are often restricted.* The connection matrices of these models contain only cortico-cortical connections within a single hemisphere. Potentially important connections to and from the contralateral hemisphere and to and from subcortical structures are excluded from the connection matrix (Mountcastle, 1998). Some of the models in figure 1 do not even include the LGN. (5) *The models are invalid with respect to latency data.* A final limitation identified by Mountcastle (1998) concerns the validity of the models in the light of latency data. According to Mountcastle, single unit recordings show that areas in different levels of the hierarchy of these models are nevertheless simultaneously activated by visual stimuli. Clearly, such simultaneous activation seems to disagree with the associated areas being at different levels in the hierarchy.

These five limitations question the validity of large-scale models of the visual system. Now, more than 20 years after the inception of the first large-scale models, novel insights and experimental results may give rise to a reconsideration of these models. In this paper, we present a method that integrates the anatomical constraints with functional (temporal) constraints extracted from more recent experimental results. Our method leads to the identification of a new structure that meets all the constraints imposed by the integrated data. Before presenting our

approach, we expand on the fifth limitation mentioned above, *viz.* the validity of current large-scale models of the visual system in the light of single unit latency recording studies (Bullier, 2001; Schmolesky *et al.*, 1998). In our method we will use the data from these studies as temporal constraints for our model.

First-spike time coding might be the only available neural mechanism to bring about rapid behavioral responses, as the alternative neural code, rate coding, is too slow for such responses (e.g. Thorpe *et al.*, 2001; VanRullen *et al.*, 2005). It has been shown that first spikes can be selective for orientation, faces and optical flow (Lamme *et al.*, 2000). Given these considerations, an analysis of the spike arrival times at various cortical areas may reveal part of the underlying functional architecture. Schmolesky and colleagues (1998) performed a study in which they measured the onset latencies of single-cell responses at several cortical areas in individual anesthetized macaque-monkey brains, evoked by flashing visual stimuli. In figure 2, we replotted the results obtained by Schmolesky *et al.* These data reveal a number of inconsistencies with the large-scale anatomical models. For instance we would expect that first spikes arrive later in areas at higher levels in a hierarchy than those in lower levels, but when comparing the latencies in figure 2 with the models in figure 1 it turns out that this is often not the case. For example, we can see that area FEF, which is in level 7 in our schematized figure 1 (it is even at level 9 of the original publication (Felleman and Van Essen, 1991)) has latencies comparable to those in V3 (level 3/4), MT (level 3-5) and MST (level 3-7). The latencies of FEF even overlap considerably with those of V1 (level 2). Schmolesky *et al.* also noted this and they concluded “our data simply indicate that the ... anatomical hierarchies fail to account for the initial flow of signals in the visual system and therefore may not accurately represent the ‘functional’ hierarchy of the visual system” (p. 3277). It seems that large-scale anatomical models of the visual system do not agree with the timing data of Schmolesky *et al.* (1998). Several others have also noted similar inconsistencies. In a review of mammalian spike timing data, Bair (1999) observed that neurons assigned to different hierarchical levels are often activated at the same time or in the wrong order with respect to their presumed hierarchical relation. In another review of the available latency data, Nowak and Bullier (1998) state that “latencies to visual stimulation in monkey are not ordered as expected from [anatomical hierarchies]” (p. 229) and they cite several studies in support of this claim. The conduction velocity in the efferent fibers also plays a role in latencies, but this alone cannot explain the discrepancies between timing data and structural data fully and determining or approximating this velocity is not possible with our current knowledge.

Figure 2: Mean onset latencies in milliseconds (y-axis) of several areas in the visual system (x-axis). For each area, its level in the hierarchical model (Felleman and Van Essen, 1991) is indicated between brackets. Data used from Schmolesky, Wang et al (1998).

Taken together, it seems that the response latencies in the visual system are incompatible with large-scale models of the known structural connectivity of the visual system. We aim at resolving this inconsistency by integrating structural connectivity data with single unit recording data. Finding networks with a connectivity pattern that fits both kinds of data might not only eliminate the observed inconsistencies, but also suggest a different model better constrained by multiple sources of data. If the model is more constrained, we might learn more about possible connections that have not been investigated yet, or have been excluded from the model. If the generated networks differ substantially (in both fit and architecture) from current models we cannot only conclude that the hierarchical model does not explain the timing data optimally, but we can also point to possible reasons. We want to do this by adopting an extendible method (it should be possible to add both new data and other kinds of data) that can use both structural and functional data as ‘converging evidence’ to model the structure of the visual system. The structural data will be extracted from a database, CoCoMac, which combines several hundred studies about the anatomical connectivity of the adult macaque brain. The functional data will be taken from a single representative study and a review article of the available latency data. To find network topologies that fit both kinds of data an optimization method called simulated annealing will be used. A schematic overview of the method can be seen in figure 3. In short, with our new method we want to arrive at a revised, more constrained model of the visual system, integrating both structural and functional data, with the additional goal of mitigating the problems of exclusion and incompleteness.

Figure 3: Schematic overview of the method used.

Methods

Our method employs the following procedure: we define a connection matrix W in which each element w_{AB} represents the presence ($w_{AB} = 1$) or absence ($w_{AB} = 0$) of a connection from area A to area B . Initially, the elements of the connection matrix are randomly assigned a value such that half of the elements is set to 1 and the remaining elements is set to 0. Subsequently, the values in the connectivity matrix are adapted using an optimization algorithm in order to minimize violations of the anatomical and functional constraints. The optimized matrix represents a connectivity pattern, i.e., a model for the connectivity of the visual system that is in agreement with the anatomical and temporal data. In what follows we describe the acquisition of the anatomical and temporal data, the criteria for data inclusion, the evaluation of candidate connectivity patterns, and the optimization algorithm.

Anatomical data acquisition

Anatomical connectivity data was obtained from the CoCoMac (‘Collation of Connectivity data on the Macaque brain’) database (Stephan *et al.*, 2001). At the moment of writing it contains the details of more than 400 studies about the anatomical connectivity of the adult macaque brain using tract tracing studies. CoCoMac represents all of this data in an objective, coordinate-free, parcellation-based fashion and enables the user to integrate contradictory findings in the literature, depending on the choice of several parameters. The advantage of using

CoCoMac over data from individual studies is that it combines hundreds of tract tracing studies into a single connectivity matrix. With a mathematical method called ORT (Objective Relational Transformation), it is possible to combine and transform brain mapping data from any parcellation scheme to a coordinate-independent freely chosen parcellation scheme (K. E. Stephan *et al.*, 2000). This allows us to combine connectivity data on areas from several parcellation schemes in one of our data sets (data set 2). The database is publicly available and can be queried through the online interface CoCoMac-Online at <http://www.cocomac.org/> (Kotter, 2004).

Timing data acquisition

We define two data sets for the timing data. The first data set is from a single study mentioned in the introduction (Schmolesky *et al.*, 1998). The data was collected from four monkeys, over a relatively large number of recording units (558) in nine areas of the brain, measured repeatedly and with a broad range of visual stimuli designed to elicit a response from the entire visual system. We obtained part of the original data from the authors and therefore we were also able to determine the variance in the data. The second data set is from a review which collected data from multiple studies (Lamme and Roelfsema, 2000, box 2 page 573). It therefore includes data on more areas than the first data set. It suits our purposes very well, as it not only includes several studies but it also weighs them as to reflect the reliability of each experimental finding.

Comparisons of timing data in the literature often suffer from differences in experimental and analytic methodologies between studies. Although the first data set is the smaller of the two, it does not suffer from these ‘incompatibility effects’, because all measurements were made within individual monkeys using common stimulus presentation and analysis techniques. This is especially important as we are interested in differences *between* latencies across the visual system. The second data set is larger than the first, allowing us to determine if the results can be generalized to larger systems. However, the data in the second data set are probably more prone to ‘incompatibility effects’ because they come from a more varied set of experiments and experimental conditions.

Data inclusion criteria

For each of the two data sets, two conditions needed to be satisfied before the data belonging to a particular brain area could be included: (1) Both first spike data and connectivity data are available. For instance, the connectivity data for Ts, Ts1, Ts2 and Ts3 were available whereas the functional data were only available for Ts. Therefore only Ts was included in the analysis. (2) Areas included in the selection should be considered part of the visual system and should not be too large to be useful in the analysis. For instance, area PreFr (prefrontal) from

Lamme and Roelfsema (2000) was excluded because it contains a very large number of other areas and because it is arguably not part of the visual system. Because the exact mapping relation between areas FEF and 8a is controversial (e.g. compare Cavada *et al.*, 1989; Felleman and Van Essen, 1991; Stanton *et al.*, 1989) we decided to exclude 8a to resolve any uncertainties.

Evaluation of candidate connectivity patterns

In order to be able to optimize the connectivity matrix, we need a numerical measure of the goodness of fit of timing and connectivity data for any given connectivity pattern. This allows us to search for the best fitting network and is essential for the used optimization technique employed. Below, we define measures for the anatomical fit and temporal fit and combine them into a single overall fitness measure.

The definition of the anatomical fit is relatively straightforward. We define the anatomical fit f_{anat} on the unit interval as the proportion of corresponding connections between a candidate connection matrix (CM_A) and the anatomical connection matrix retrieved from CoCoMac (CM_B), i.e.:

$$f_{anat} = \frac{\text{number of corresponding connections between } CM_A \text{ and } CM_B}{\text{total number of connections in B}}$$

When f_{anat} is 0 there are no corresponding connections between A and B (worst fit), and when f_{anat} is 1 both are in complete agreement (best fit). Note that the fit will decrease when a connection that is established absent in CM_B is present in CM_A , but the fit will be unaffected when a connection that is empty CM_B is present in CM_A . This implies that violating an established absent connection constraint is treated identical to violating an established existing connection.

The temporal (latency) fit, f_{lat} , is defined as a linearly transformed Pearson product-moment correlation coefficient (PMCC). It expresses the similarity between (the order and magnitude of) the timing data and our simulated timing data (see below). The function f_{lat} should provide an indication of the degree to which the orders of activation of nodes in two networks agree. Although rank correlation seems more appropriate for the simulated timing data because they contain ordinals, the use of rank correlation would mean losing all sensitivity to distances between latencies and therefore PMCC is used because it accommodates the continuous values of the real timing data, which is measured at the ratio level. The minimum value of the PMCC is -1 (worst fit) and the maximum is 1 (best fit). Because f_{anat} has a range of 0 to 1 and we want f_{lat} to have the same range we apply a linear transformation so that:

$$f_{lat} = \left(\frac{PMCC}{2} \right) + 0,5$$

In order to simulate the timing data for our candidate connection patterns, we employ a version of the “shortest path” algorithm (Dijkstra, 1959). We start by determining the node that receives the initial input (the seed node). This node is defined as being active at the first time step ($t = 1$). We then use the following function to propagate activity through the network for $t > 1$:

$$a_i(t) = f\left(\sum_{j=1}^N w_{ij} a_j(t-1)\right) \quad f(x) = \begin{cases} 0 & \text{if } x = 0 \\ 1 & \text{otherwise} \end{cases}$$

where $a_i(t)$ represents the activity of node i at time t and w_{ij} the element of the connection matrix, i.e., the connection from node i to node j representing the presence ($w_{ij} = 1$) or absence ($w_{ij} = 0$) of a connection. Nodes connected to an active node will be active the next time-step and will remain active afterwards ($w_{ii} = 1$, for all i). If all nodes of the network are active, each node is assigned a level equal to the number of connection steps from the seed node. In all simulations, the number of time steps is sufficiently large to allow activations to propagate through the entire network.

The overall fit function F is defined as the weighted sum of both fitness measures, i.e.:

$$F = \alpha \cdot f_{anat} + (1 - \alpha) \cdot f_{lat} \quad \text{where } \alpha \in [0,1]$$

The two measures of fit are weighted by factor α .

Optimization algorithm

The optimization algorithm used in our method is simulated annealing. Simulated annealing is a stochastic combinatorial optimization algorithm belonging to the class of methods known as gradient descent algorithms. What makes it especially suited for our needs is that it is capable of finding solutions that obey multiple types of constraints. In addition it is generic in that it does not require an explicit knowledge description of the problem at hand (Zomaya *et al.*, 1999). The simulated annealing algorithm was first described by Kirkpatrick, Gelatt *et al.* (1983) and has been applied before for optimizing features of cortical networks (Kaiser *et al.*, 2006). In our method, the algorithm makes changes to individual elements of the connection matrix by applying the rule that each change should increase the fitness. The algorithm varies the strictness with which the rule is applied. Initially, the degree of randomness (or *temperature* T) is high, meaning

that changes that decrease the fitness are also allowed, and the values of individual elements are updated at random. As time progresses, the degree of randomness is lowered towards full determinism (i.e., zero temperature). At this stage, connections are updated by applying the rule strictly. The quality of the final solution (i.e., the agreement with the anatomical and temporal constraints) depends on the rate of change from randomness towards determinism. The annealing schedule defines the rate in terms of the time-dependent temperature $T(n)$:

$$T(n) = \tau \cdot T(n-1)$$

where n is the iteration step of the algorithm, and τ is the annealing factor. By allowing changes that reduce fit during early iterations of the algorithm while later making these changes very improbable, the use of temperature allows the algorithm to avoid local minima, i.e., solutions that fulfill a subset of the constraints but are not the optimal solution. Other gradient descent algorithms could have gotten ‘stuck’ in these local minima because multiple connections need to be flipped to result in an increase of the fitness.

The employed method makes it possible to generate networks that fit both timing and connectivity data without any need for assumptions about hierarchy or connectivity.

Figure 3 presents a schematic overview of our method. The latency data (shown on the left) and the anatomical data (shown on the right) are transformed into constraints. Starting from a random connectivity pattern, the simulated annealing algorithm (shown in the middle) uses both types of constraints to generate candidate connectivity patterns that obey the constraints. Our method can be used with any selection of brain areas and can easily be extended to include newer data as it becomes available. Other kinds of data can also be added with relative ease as long as a fitness function can be devised for it.

Parameters

We used the following parameters for the optimization algorithm in all our simulations. The initial temperature was $T(0) = 4$ and the annealing factor was set to $\tau = 0,99$, the maximum number of annealing iterations was set to 1500, and the parameter α was set to 0,5 so the contribution of timing (f_{lat}) and connectivity (f_{anat}) fit to the total fitness was balanced. It should be noted that the two measures of fit, f_{anat} and f_{lat} , are not necessarily equally sensitive to changing the state of one connection. For every solution we ensured that when the algorithm terminates, at least hundred iterations of the simulated annealing algorithm had not lead to new solutions.

We repeated all our simulations to show that the results are stable over a wide range of values for the above parameters. We varied the values of α , $T(0)$, τ . We also varied the amount of connections in the randomly generated network that serves as the starting point for the annealing algorithm (initial edge density). For α and initial edge density the range could be varied over the entire possible range. The results of these tests can be seen in figure 4. Except for the drop-offs at extreme values of α and a few small peaks, the results are essentially stable over the entire range of the parameters. The drop-offs are a result of the fact that at extreme values of α , the networks are fitted to one fit function only (either f_{lat} or f_{anat}), instead of to two. The small peaks are sub-optimal solutions that disappear after the averaging of results described in the next section.

Analysis of the Results

Because the optimization method described above is stochastic, some form of averaging over multiple solutions is needed. In our method, multiple solutions are multiple connection matrices. All our results are based on 1000 computed optimal connection matrices, each using different initial connection matrices. All the matrices can be summarized into one matrix by defining each element as a probability of the presence of a connection. When a number of solutions are generated by our method, two types of values will be found in the cells. The first type does not change when increasing the number of solutions, and these values are always 100 or 0 percent. The values of 100 and 0 percent represent connections that were present or did not exist, respectively, in all the simulations. The second type has a value that asymptotically moves closer to an intermediate percentage. For instance, the value of 50 percent means that this particular connection is present in half of the solutions and, presumably, does not matter for the fit of this network. These connections are connections that were not constrained by our data; they have not been researched according to CoCoMac (Kotter, 2004) and do not matter for the first spike timing in the network (e.g. they could represent a feedback connection instead of a feedforward connection). When we excluded all the solutions that are not optimal (as expressed by the amount of total fit with the data) all elements have values of 0, 50, or 100 percent. The resulting connection matrices therefore only contain the values 0 (0%) 1 (100%) or they will be empty (50%).

The computational tools needed to import the data from the CoCoMac database (Cocomac Import/Export Tool) and the tools to perform the optimization and analyze the data (BrainAnnealer) are custom programs written in Object Pascal with the Borland Delphi compiler. Tools, source and documentation together with the data used can be downloaded at www.capalbo.nl.

Figure 4: Illustration of the parameter sensitivity of the model. Each graph shows the anatomical and latency fits (vertical axis) as a function of the parameter value. The varied parameter, the range of variation and the parameter actually used in the results are listed in the first column, the total fit for the first dataset is plotted in the second column and the fitness for the second dataset is plotted in the last column. Within each plot, the black line represents the anatomical fit and the white line represents the latency fit.

Results for data set 1

In the first data set we included the areas used in the study by Schmolesky, Wang *et al.* (1998). This data set contains 8 areas: LGN, V1, V2, V3, V4, MT, MST and FEF. The LGN is the node of the system that receives the first input, the seed node. Note that because we are only studying bottom-up processing, any subcortical area can play exactly the same role as the LGN in the dynamics of the system. Therefore we will call this node SCA (Sub Cortical Area). As we will see later, subcortical areas such as the superior colliculus and pulvinar are also likely candidates for this role. The connectivity data were extracted from the CoCoMac data base (Kotter, 2004) in the form of an 8 by 8 connectivity matrix.

To \ From	SCA	MT	FEF	MST	V3	V2	V4	V1
SCA								
MT	1*			1	1	1	1	1
FEF	1*	1		1	1	1	1	0
MST	1*	1	1		1	1	0	1
V3	1*	1		1		1	1	1
V2	1*	1		1	1		1	1
V4	0*	1		0	1	1		1
V1	1	1	0	0	1	1	1	

Figure 5: Results for Data set 1, connectivity entries not in the original connectivity matrix have been marked with an asterisk (*).

The resulting average connection matrix is shown in figure 5. New connection entries (as compared to the original connection matrix) have been marked with an asterisk. New connections from the SCA have been added to almost every area in the network, except to V4. (The connection to V1 was already present.) In figure 6 the measures of fit f_{anat} and f_{lat} of our resulting network are compared to those of the most influential large-scale structural model, hierarchical model (Felleman and Van Essen, 1991). The connectivity and timing costs of the hierarchical model are compared to the costs of the new resulting connectivity matrix. Our network clearly fits the data better. The structural fit (meaning the fit of the network with the known structural data) is maximal ($f_{\text{anat}} = 1$) for the solution. This means that our network does not have any connections that are incompatible with the known tract tracing data. There is an increase in the temporal fit with respect to the hierarchical model, implying that our network fits the available timing data better than the hierarchical model. Simply put: the newly generated network explains the first spike timing data better without violating any constraint from the known tract tracing data. Figure 7 depicts our solution superimposed on an actual macaque brain. The newly introduced connections are colored. It is clear that a subcortical route has been added to accommodate the temporal constraints. As we shall argue in the discussion this finding confirms Mountcastle's (1998)

suspicion that subcortical routes play a significant role in cortical connectivity and agrees with recent connectivity studies.

Figure 6: The fit of the hierarchical model by Felleman & Van Essen (1991) compared with the fit of the network generated by our method using data set 1.

Figure 7: Best-fit connectivity superimposed on an MR-image of the macaque brain. MR-image courtesy of R.Goebel and N.K. Logothetis, rendered with BrainVoyager© software. Added connections are red.

Results for data set 2

In our results with data set 1 we have shown that the method works for a small data set from one parcellation scheme. With data set 2 we want to use our method on a larger data set, with more areas from different parcellation schemes (using ORT, K. E. Stephan *et al.*, 2000), hoping to increase the validity of our claims.

Also, a larger data set might increase the constraints on the model. The first spike time data chosen for this purpose were those of Lamme & Roelfsema (2000). After applying the inclusion criteria, we used the data for the following 27 areas: SCA, V1, 7ip, V3, Ipa, Pga, TE2, TE3, 5, 7a, FEF, FST, MST, MT, SEF, SMA, V2, V4, MI, TS, TAa, TE1, TEa, Tem and TPO. The resulting connection matrix can be seen in figure 8. New cell entries that differ from the original connectivity matrix have been marked. The connections added to the matrix as a result of including the constraints of the timing data are again mainly connections from the Sub-Cortical Areas (SCA). New cell values also show that some connections have to be absent in order to account for the timing data. In figure 9 the fits of the most prominent large-scale model, the hierarchical model (Felleman and Van Essen, 1991), and our network are compared. Again, the connectivity and timing costs of the hierarchical model are compared to the costs of the new resulting connectivity matrix. The anatomical fit is at its maximum value of 1, meaning that the resulting network is in complete concordance with the known anatomical data. Our network is clearly an improvement over the hierarchical model regarding the fit with the latency data (an increase from 0,67 to 0,93). These results indicate that adding sub-cortical routes to the network yields a substantial increase of the timing fit. These results establish that the inclusion of the subcortical routes is also essential for explaining latencies in large visual networks.

As mentioned in the introduction, one of the shortcomings of the large-scale structural connectivity models is their indeterminate organization, most notably the indeterminate organization of the hierarchical model (Hilgetag *et al.*, 1996). Our method integrates two types of constraints, thereby reducing the ‘indeterminateness’. To confirm the reduction of indeterminateness, 100 solutions were analyzed to determine the levels at which individual areas were placed. Subsequently, we determine the average level (and variance) of each area. Figure 10 shows the results of this analysis. In the left-most part of figure 10 we can see that when using our method with anatomical constraints only, we get roughly the same indeterminate organization as observed for the hierarchical model, even though we used a different cost function than was used in the original publication. Areas can be at multiple levels without violating the anatomical constraints as Hilgetag, O'Neill *et al.* (1996) have pointed out. The right part of figure 10 shows the results for the combined temporal and anatomical constraints. The number of candidate hierarchies is reduced considerably. More areas are confined to a single level of the hierarchy, and the remaining areas have a smaller number of possible levels to which they can be assigned. Overall the determinateness (or constrainedness) is greatly improved due to the inclusion of timing data.

	SCA	V1	7IP	V3	IPA	PGA	TE2	TE3	5	7A	FEF	FST	MST	MT	SEF	SMA	V2	V4	MI	TS	TAA	TE1	TEA	TEM	TPO
SCA																									
V1	1		0	1	0	0	0	0	0	0	0	0	0	1			1	1	0			0	0	0	0
7IP	1*	1		1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	1
V3	1*	1	1		0	0	0	0	0	0	1	1		1			1	1	0	0	0	0	0	0	0
IPA	1*	1	0	1		1	1	0	0	1	1			1			1	1	0	0		0	0	0	0
PGA	1*	1	0	1	1		0	0	0	1	1	1		0	0		0	1	0	1	0	0	0	0	0
TE2	0*		1		1	0			0	1	1	1	0	1			0		0	0	0	1		1	0
TE3	1*				1	1			0	1	1	1	1	1			1		0	0	0				0
5	0*	0	1	0	0	1	0	0		1	1	1	1	1	1	1	1	0	1	0	1	0	0	0	1
7A	1*	0	1	0	1	1	1	0	1		1	1	0	0	1		0	0	0	0	0		0	0	1
FEF	1*	0	1		1	1	1		1	1		1	0	0	1		0	1	0	0	1				1
FST	1*	0	0	1		1	1	0	0	1	1			1			0	1	0	0	0	0	0	0	0
MST	1*		0				0		1	0	1	0		0			0	0	0	0	0		0	0	0
MT	1*	1	1	1	1	0	1	0	0	0	1	1	1		0		1	1	0	0	0	0	1	0	0
SEF	1*		1				0		1	1	1						0		0						
SMA	1*		1						1								0		1						
V2	1*	1	1	1	0	1	1	0	1	0	1	1	0	1	1			1	0	0	0	0	0	0	1
V4	1*	1	1	1	0	0			0	0	1	1	1	1			1		0	0	0		0	0	0
MI	0*	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0		0	0	0	0	0	0
TS	1*		0		0	0	0		0	0	1	0	0	0			0	0	0		1		0	0	1
TAA	1*		0		1	1	0		0	0	1	1	1	1			0	0	0	1			0	0	
TE1	0*				1	1	1		0	1	1	1	1	1			1		0	0	0		1	1	0
TEA	1*		0	0	0	0	1	1	0	1	1	0	0	0			0	0	0	0	0	1			0
TEM	1*	1	0	0	0	0	1		0	1	0	0	0	0			1	0	0	0	0	0			0
TPO	1*		0		0	0	0		1	1	1	0	0	0			0	0	0	1			0	0	

Figure 8: Results for Data set 2, connectivity entries not in the original connectivity matrix have been marked with an asterisk (*).

Figure 9: fit of the hierarchical model by Felleman & Van Essen (1991) compared with the network generated by our method using the data set 2. Results graphed in the same manner as in Figure 6.

Figure 10: Comparison of the distribution of areas (y-axis) over the levels in the hierarchy (x-axis) in 100 solutions. On the x-axis is the average level an area is assigned to $\pm$ two standard deviations. On the left side the distribution is given without the areas being constrained by the latency data. On the right the distribution is given when the timing constraints are used. The area names are preceded by the parcellation scheme in which they are used, separated by a hyphen (CoCoMac notation).

Discussion

This paper presented a data-driven method to generate plausible models of cortical connectivity between areas of the visual system based on a combination of anatomical and temporal data. Our results show that connectivity patterns with subcortical routes fit the timing data of the visual system better than those without subcortical routes, such as the hierarchical model (Felleman and Van Essen, 1991).

Advantages of the model

One of the strong points of the method used is that it is completely data driven. Large-scale network architectures can be generated with one main assumption only: the time it takes for a signal to pass from one area through the afferent pathway to another area can be treated as a unitary whole. We do not need to rely on any assumptions about the structure or the hierarchy of the areas in the network. One of the possible pitfalls of neural networks models is that the complexity of the model does not add to the predictive power of the model. Sometimes models require setting many parameter-values of which the validity is hard to ascertain. In our method there are only four annealing parameters that need to be set to perform an analysis, the effect of these parameters are well-known (Kirkpatrick *et al.*, 1983) and the results do not depend critically on the specific parameter settings, as we can see in figure 4. See Methods, Optimization for more details.

Possible additional constraints

Our method combined two types of constraints derived from connectivity and timing data, which is more than the single type of constraint used in earlier work (Felleman and Van Essen, 1991; Young *et al.*, 1994; Zeki and Shipp, 1988). One might argue that more than two types of constraints may or need to be included to generate even more plausible models of cortical connectivity. We mention three additional types of constraints: (1) the conduction velocity, (2) the inter-area distance and, (3) variance in spike time latencies. Although the inclusion of additional types of constraints is rather straightforward in our method, we also motivate why we did not include them in our method.

1. *Conduction velocity.* One might argue that conduction velocity is a possible additional constraint that needs to be added in our method, because it affects the first spike latencies. For instance, the relatively early response of area FEF could be due to a high conduction velocity in the fibers leading to FEF, rather than due to the existence of a direct route to FEF. We argue that it is not beneficial to add conduction velocity as a constraint to our method for three reasons; (I) it cannot explain the latency data fully, (II) data on cortico-cortical conduction velocities are scarce, and (III) conduction velocity cannot be reliably estimated. We will elaborate briefly on these reasons. (I) *Differences in conduction velocities cannot fully account for the inter-area latency differences.* In the hierarchical model (Felleman and Van Essen, 1991) for instance, areas separated by one level or more have extremely small differences in first-spike latencies (e.g. MST – FEF differ in 1 level and 1 ms in latency; V1 – MT differ in 4 levels and 5 ms in latency, whereas V1-V2 differ in 1 level but 18 ms in latency) and sometimes the latencies are even reversed (e.g. V4 - FEF). This also holds when the hierarchy is based on the shortest possible route to connect two areas like the model used by Petroni, Panzeri *et al.* (2001). (II) *Relatively little is known about conduction velocities of cortico-cortical connections* (Nowak *et al.*, 1997). Most of our knowledge on conduction velocities stems from neural cells outside of the cortex and was not investigated in mammals. This limitation is aggravated by the fact that conduction velocities differ substantially between cortical and subcortical pathways (Salami *et al.*, 2003) and species (cf. e.g., compare Nowak, James *et al.* (1997) with Girard, Hupe *et al.* (2001)). (III) *The conduction velocity cannot be reliably estimated.* One might argue that even if the actual conduction velocities between areas have not been measured, they may be generalized from an estimation of the conduction velocities in an entire functional stream (e.g., the magno- and parvo- cellular streams). We argue that knowledge of the conduction velocity of different cell types in different functional streams does not automatically lead to a reliable estimate of the conduction velocity. Conduction velocity is dependent on myelination

and the diameter of neurons and these are known to differ for different cell-types. Different cell-types are associated with different functional streams and therefore conduction velocity might differ per functional stream. However, the number and nature of functional streams in the visual system and their constituent cell types are debated (e.g. see Goodale *et al.*, 1992; Livingstone *et al.*, 1988; Sincich *et al.*, 2005; Van Essen *et al.*, 1996). It is unclear how the conduction velocity of connections between areas within one functional stream or between two functional streams could be estimated. The fuzzy demarcation of the functional streams and the lack of knowledge about how the conduction velocities of different cell types ‘add up’, make any estimation quite unreliable. Despite the current limited knowledge on conduction velocities, it would be interesting to study the effect of conduction velocities by systematically varying conduction velocities in a model where all else is constant and we plan on doing this in future work. To sum up, conduction velocity probably does play a role in latencies, but we did not add it as a constraint because it cannot explain the discrepancies between timing data and structural data fully, data on cortico-cortical conduction velocities is scarce, and any approximation of the conduction velocity in a functional stream is unreliable.

2. *Inter-area distance.* Another constraint that might influence the spike timing is the distance between areas. It is important to note that the Euclidean distance between areas represent the lower bound on the true inter area distance. Actual inter-area fibers must follow the sulci and the gyri, in effect increasing their lengths beyond the Euclidian distance. To the best of our knowledge, actual inter-area fiber distances are not known. However, Kaiser and Hilgetag (Kaiser and Hilgetag, 2006) have shown that only a small percentage of the connections in the macaque brain are curved so that Euclidean distances might be a good approximation of true inter-area distances. But even when trying to ascertain true inter-area distances some problems remain. One of these problems is the use of Objective Relational Transformation (ORT) (K. E. Stephan *et al.*, 2000) as is done for dataset 2. ORT transforms multiple areas from multiple parcellation schemes into areas in a single coordinate free scheme. As a consequence, information on absolute distances is lost. Therefore, the inter-area distances for data set 2 cannot be determined. Another problem is that, for reasons mentioned above in the context of conduction velocities, inter-area distance *differences* probably do influence timing, but not to the extent that it can explain latency differences. Overall, inter-area distance was not used as an additional constraint because true distances are not yet known, measuring distances between areas from different parcellation schemes is problematic and it is unlikely that inter-area distance differences could explain large latency differences.

3. *Variance*. Latencies vary across multiple replications under the same experimental conditions. In our method, the simulated spike times are deterministic and fall within discretized intervals. Given an average latency, the variance represents a measure of certainty on the spike times. Larger variance implies more uncertainty about the actual latency and relaxes the associated timing constraint. Variance might have been incorporated as an extra term in the evaluation function for data set 1 (for which variances are available), but not for data set 2. The data in this set are obtained from a meta analysis of from multiple studies (Lamme and Roelfsema, 2000). The raw data from the original studies used in the meta-analysis or data from another review paper (e.g. Nowak and Bullier, 1998) might have been used here, but then we would also have lost the advantages of weighing the data (see Lamme and Roelfsema, 2000).

Resolving inconsistencies

Do our results really solve the inconsistencies between the latency data and the earlier anatomical models? Clearly, if a model agrees with latency data, all the areas assigned to higher levels of the hierarchy should have longer latencies than those assigned to the lower levels. In figure 11 the timing data is plotted as a function of the level an area is in. This is done for the hierarchical model (Felleman and Van Essen, 1991) (10a and 10c) and for our network (10b and 10d). In figures 10a and 10c the sequence of the first spikes does not follow the levels, once again illustrating the shortcomings of all earlier large-scale models. For instance, in figure 11a, FEF and V4 pop-out as areas with ‘wrong’ timing for their position in the hierarchy. Figures 10b and 10d show that the networks generated by our method do not suffer from this shortcoming; each area is assigned to its appropriate temporal level. As is evident from figures 10b and 10d, our solution has three levels only.

Alternate explanation of the latencies

We have argued that our results solve the inconsistencies between the latency data and earlier anatomical models. An earlier study has attempted to show that these inconsistencies do not exist (Petroni *et al.*, 2001). Petroni, Panzeri *et al.* simulated the cortical network of the areas examined by Schmolesky *et al.* (1998), using the connectivity matrix of the hierarchical model (Felleman and Van Essen, 1991). However, Petroni, Panzeri *et al.* (2001) used something they call the hodology (Nicolelis *et al.*, 1990), i.e. the shortest possible route to connect two areas, to determine the level at which an area is placed, instead of the levels of the earlier models (Andersen *et al.*, 1990; Distler *et al.*, 1993; Felleman and Van Essen, 1991; Zeki and Shipp, 1988). Their simulated latencies resemble the real latencies. They conclude that hodology correlates better with latency than the

hierarchical organization. However, our work shows that even the hodological hierarchy can not explain the latencies fully. In the results of Petroni, Panzeri et al. (2001) it is already evident that the timing in areas FEF and V4, prominent dorsal and ventral areas, do not fit the model. In their own words: “two areas where we found some disagreement between simulated and experimental latency were FEF ... and V4”. Furthermore, as we have argued earlier, even a hierarchy based on hodology cannot explain the extremely short latencies or ‘reversals’ in the latencies. Our results show that the hodological hierarchy cannot explain the overall latencies optimally. In figure 11 we have shown that even when hodology is considered (the topology we use is always based on the shortest route) the hierarchical model remains incompatible with the latencies. We shall argue below that our explanation provides a better alternative, because it addresses some of the limitations of previous models and might explain some functional characteristics of the human visual system.

Figure 11: Comparing the hierarchical model (Felleman and Van Essen, 1991) with the networks generated by our method, with regard to latency. On the x-axis is the level in the hierarchy an area is in when only considering the shortest possible route from the source node. On the y-axis is the first spike latency in ms. Area names (indicated as in figure 10) are included for general reference, overlapping labels omitted for clarity. Areas in a higher level in a hierarchy should have longer latencies than areas lower in the hierarchy.

The importance of subcortical connections

For both our data sets, the most prominent and remarkable result is the large increase in goodness of fit with the latency resulting from the introduction of direct connections from the subcortical areas (SCA) to the cortical areas, bypassing V1.

Such direct connections are typical long-distance projections. It has been suggested that the brain shows strict optimal component placement and therefore only has short projections between adjacent brain areas. However Kaiser and Hilgetag (Kaiser and Hilgetag, 2006) noted that long-range projections also exist and that they have an essential role to play, e.g. in the minimization of processing steps. Our findings demonstrate this principle perfectly.

Additional analysis reveals that discarding all subcortical areas from the data set, the best fit is to connect all extrastriate areas to V1, with the exception of V4. Although the resulting connectivity pattern is still superior in terms of fitness to the hierarchical model (i.e., $f_{\text{anat}} = 0,947$, $f_{\text{lat}} = 0,871$) the fits are still smaller than those obtained in our main solution. Apparently subcortical pathways explain the data better than cortico-cortical ‘shortcuts’.

The importance of the subcortical route has been recognized before in various publications. Lamme and Roelfsema (2000) noted that a reason for the lack of correspondence between the hierarchical organization and the response latencies might be that subcortical structures like the LGN, the superior colliculus (SC), and the pulvinar (PUL), also project to various extrastriate areas. Even Petroni *et al.* (Petroni *et al.*, 2001), who claim there is no large discrepancy between latencies and the hierarchical model, propose that the extremely fast response in FEF might be caused by a subcortical connection through the superior colliculus. It is known that not only the LGN, but also the PUL and the SC have retinal inputs (Grieve *et al.*, 2000 ; Perry *et al.*, 1984; Rodieck *et al.*, 1993), making direct connections from the cortex to these areas true shortcuts from the retina.

With the additional help of the CoCoMac database (Kotter, 2004) and Objective Relational Translation (ORT) analysis (K. E. Stephan *et al.*, 2000), a literature search was done to assess the connections from the subcortical areas suggested above, to the cortical visual areas named in our results. Except for the obvious connections to V1, the LGN is also connected to V2 (Bullier *et al.*, 1983). The pulvinar is a structure that is densely connected to cortical areas, i.e., it is connected to V2 (Benevento *et al.*, 1976), V3 (Rockland *et al.*, 1999), V4 (Adams *et al.*, 2000), MST (Boussaoud *et al.*, 1992) FEF (Romanski *et al.*, 1997) and MT (Sincich *et al.*, 2004). Interestingly, MT not only resembles an early visual area because of this subcortical connection but it is also an early visual area in the way

that it matures (Bourne and Rosa, 2006). Although earlier studies repeatedly suggested the SC might be connected directly to the visual cortex (Petroni *et al.*, 2001; Rodman *et al.*, 1990), little structural evidence for the existence for such connections was found. Relatively few studies have addressed the presence of these connections. A connection from the SC to V1 exists (Graham, 1982), but connections to the following visual areas were examined but not found: V2 (Ungerleider *et al.*, 1984), V3 (Beck *et al.*, 1998), PO (Benevento and Rezak, 1976), IT (Webster *et al.*, 1993). A possibility is that the SC is involved indirectly by feeding input to the pulvinar (Lysakowski *et al.*, 1986) or that it is connected via the mediodorsal thalamus (Sommer *et al.*, 2004). Summarizing, the subcortical routes suggested by our results are in line with the above findings as all ‘new’ subcortical connections (connections from SCA in the figures) found in the results from dataset 1 have been confirmed by anatomical research. These routes run through the lateral geniculate nucleus and the pulvinar (but not through the superior colliculus). The fact that the predictions made by our method have been verified validates our method and lends credibility to our results.

Subcortical pathways appear to play a larger role in the propagation of the visual signal than was assumed before. More specifically, the connections from subcortical areas to extrastriate areas have been left out of most models of the visual system. Therefore these connections need to be considered in any future description of the structure of the visual system.

Figure 12: Hierarchy proposed in this article with the areas from data set 1. Comparable with figure 1.

Towards a new model

Because of all the reasons described above we propose a new, revised organization of areas that is based on both timing and structural data (See figure 12). It is important to note that the organization proposed here is based on two kinds of data only, and as such only reflects the combination of first spikes and structural connectivity. Therefore, it can not claim to explain other aspects of hierarchy like the increasing complexity of visual responses or receptive field size. In how far the organization we propose reflects the ‘general organizational principle’ (if such a thing exists at all) might be dependent on the importance of

the processing of first spikes compared to all processing in the cortex. It might well be that the inclusion of other kinds of data (e.g. receptive field size) will reorder the organization. Another possibility is that in order to explain different kinds of data, different organizations are necessary, and no single organization exists that can explain all aspects of the visual system.

Human visual system

Our study is entirely based on connectivity and timing data from the macaque visual system. What does our work tell us about the structure of the *human* visual system? Although the homologies between monkey and human visual cortex remain uncertain for some areas, one of the main reasons for studying the monkey visual cortex are the clear similarities with the human visual cortex (Sereno *et al.*, 2005). All the areas from data set 1 have a more or less clear homology in the human brain (Orban *et al.*, 2004; Tootell *et al.*, 2003) enabling at least some generalization from our results to the human visual system.

Our results, when generalized to the human brain, might explain some recent findings in humans. Goebel *et al.* (2001) looked at the functioning of the dorsal and the ventral stream in two blindsight patients with long-standing post-geniculate lesions (FS and GY). These patients show close to normal brain activity in hMT+ and V4 although a large part of V1 has been destroyed. Similar results were found in a patient with hemianopia in the entire right visual field, who could still report movement and color change in his blind hemifield (Riddich syndrome). fMRI activity was reported in V4/V8 and V5 in the lesioned hemisphere and MEG recording showed it preceded V2/V3 activity (Schoenfeld *et al.*, 2002). A functional connectivity study showed that there was a flow of information from V5 to V4 and V2 (Hinrichs *et al.*, 2006). How can areas higher ‘upstream’ in the visual system be activated normally when almost all of their input from lower levels has been cut? Subcortical pathways like the ones suggested by our simulations, originating in LGN and the pulvinar might play an important role in explaining the residual functioning of the brain in blindsight and Riddich syndrome.

Future work

To further understand the structure of the visual system, future work should include attempts to complete the subcortical pathways in the connectivity matrices. This goal might be reached by adding existing tract tracing studies to the CoCoMac connectivity database (Kotter, 2004) or by doing new tract tracing studies into subcortical pathways. It would also be very helpful for our understanding of the large-scale structure of the visual system to see more latency studies like the one done by Schmolesky *et al.* (1998) with more areas. This would allow us to use the current method without having to rely on the

‘averaging’ methods currently used in data set 2 (from Lamme and Roelfsema, 2000). Our current approach could also be aided by more research into conduction velocities in the cerebral cortex, the exact role of conduction velocities in explaining latency data remains an open question. A modeling study similar to this one using conduction velocity as an (extra) constraint might help to resolve this question.

Conclusion

By combining data from both structural connectivity and spike timing experiments using a data driven method with few assumptions and parameters, topologies that fit both kinds of data have been found. The results show the necessity of subcortical routes to explain spike-timing data. Review of the literature demonstrates that most of the connections predicted by our method appear to exist. Furthermore we show that we are able to further constrain our model, in effect reducing the problem of indeterminacy associated with previous models (Hilgetag *et al.*, 1996). We conclude that our method successfully incorporates structural and functional data to arrive at a new large-scale model of the visual system that underscores the importance of subcortical routes.

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Chapter 3

Mapping the Large-scale Functional Structure of the Visual System with Magnetic Resonance Imaging

This chapter is based on:

Capalbo, M., and Goebel, R. (2008). Mapping the Large-scale Functional Structure of the Visual System with fMRI. *In preparation*

Abstract

In order to understand the distributed and cooperative functions of the visual system it is essential to understand its large-scale functional structure. In this study the large-scale structure of the visual system is mapped by using functional localizers to determine the location and the extent of a large number of subcortical and cortical areas in the visual system. Using functional Magnetic Resonance Imaging (fMRI) we succeeded in localizing the Lateral Geniculate Nucleus (LGN), the Superior Colliculus (SC), the Pulvinar (PUL), V1, V2, V3, V3A, VP, V4v, hMT+, FEF, FFA, PPA, LOC, and (to a lesser degree) V4 proper. Based on these results, problems that occur when delineating the FEF and the early visual areas are discussed, together with possible solutions. Additionally, localizing subcortical areas with a saccade task proved to be more reliable than using the retinotopic stimuli commonly used. All in all, a large number of areas from the visual system is reliably mapped in individual subjects in ‘original space’. This allows defining subject-specific regions-of-interest (ROIs) as a starting point for studying the effective, functional and structural connectivity of the visual system.

Introduction

Understanding what constitutes the essential elements of the brain and how these elements are connected is the key to understanding the neural basis of perception. The most apparent way to subdivide the brain into its essential elements is to look at its anatomical structure. To reveal the function of the brain, it is helpful to study the functional subdivision or *modularity* of the brain. Although there are several forms of modularity (Geary *et al.*, 2002), we will define a module as an encapsulated processing component, dedicated to perform a specific cognitive function. The way the brain is subdivided has implications for the study of connectivity within the brain. There is a large conceptual difference between a connection linking two anatomically defined structures and a connection linking two functionally defined modules. This does not only apply to structural connectivity but also, or even more so, to effective or functional connectivity. Without knowledge of the functional structure of the brain we can never be quite sure exactly what areas a connection is linking, or when that connection is used. To sum up, to understand visual perception we must understand the connectivity in the visual system and in order to understand this connectivity we must understand the functional structure of the visual system. The work presented here sets out to map this large-scale functional structure of the visual system.

Connections from deep brain structures

Substantial work has been done to reveal the functional modularization of the visual system in the brain. These studies were limited in the number or nature of the modules considered. Moreover deep brain structures, such as the LGN, are often excluded from large-scale functional descriptions of the visual system (Mountcastle, 1998). This exclusion may be motivated by the generally adopted assumption that these deep brain structures are simple ‘relay stations’. Several studies suggest that this assumption is no longer appropriate. For instance, the LGN has been shown to play an important role in the top-down stage of visual processing (Casagrande and Ichida, 2002; Koch, 2004a; Lamme and Roelfsema, 2000), the Superior Colliculus is involved in saccadic eye movement (Wurtz and Albano, 1980) and the Pulvinar is involved in signaling saliency (Grieve *et al.*, 2000).

Connections between deep brain structures and higher visual areas, bypassing the early visual areas, might explain some recent paradoxical results in humans and monkeys. A recent modeling study (Chapter 2) has shown that such connections could explain the relatively early arrival of neural signals, as measured with single cell recording, in higher visual areas such as FEF in monkeys (Lamme and Roelfsema, 2000; Schmolesky *et al.*, 1998). Other work on human hemianoptic or blindsight patients has shown that despite unilateral lesions in early visual areas,

activity in the higher visual areas of the damaged hemisphere can still be close to the activity of the normal undamaged hemisphere (Goebel *et al.*, 2001; Schoenfeld *et al.*, 2002) and that the activity in the higher visual areas precedes residual activity in the spared parts of the early visual areas in these patients (Hinrichs *et al.*, 2006). These phenomena might also be accounted for by direct connections from deep brain structures to higher visual areas, yet these connections have never been studied in this context. The main obstacle for studying these connections is that it requires a reliable localization of the deep brain areas. Early visual areas (e.g. see Goebel *et al.*, 2001; Linden *et al.*, 1999; Sereno *et al.*, 1995; Sereno *et al.*, 1994; Warnking *et al.*, 2002) and higher visual areas (e.g. see Epstein *et al.*, 1998; Kanwisher *et al.*, 1997; Malach *et al.*, 1995; McKeefry and Zeki, 1997; Petit *et al.*, 1997; Tootell *et al.*, 1995) have already been localized successfully repeatedly using functional methods and recent work has shown that functional localization of deep brain structures is also possible (Kastner *et al.*, 2004; O'Connor *et al.*, 2002; Schneider *et al.*, 2005; Schneider *et al.*, 2004).

Mapping the large-scale structure of the visual system

In the present study, we used functional magnetic resonance imaging (fMRI) at 3 Tesla to investigate the large-scale functional architecture of the visual system and its subsystems with high spatial resolution. This detailed functional architecture, once established, is an indispensable starting point to study the large-scale connectivity of the human visual system. Some methods to ascertain connectivity place limits upon the way that anatomical and functional data can be transformed or normalized. Therefore, in this study, we will localize all areas in original space (as opposed to e.g. Talairach space, Talairach *et al.*, 1988). While this makes a quantifiable comparison between subjects difficult it enables us to quantify true-subject specific parameters, such as the volume of the localized areas.

We will attempt to localize deep brain structures, primary visual and higher visual modules in humans with functional MRI. To identify these areas we will adopt the terminology of Felleman and Van Essen (1991). The deep brain structures we will look for are the Lateral Geniculate Nucleus (LGN), the Superior Colliculus (SC) and the Pulvinar (PUL). We will call this specific collection of visual deep brain structures *subcortical* structures for the remainder of this chapter. The subcortical structures were chosen because of their possible role in explaining the relatively short latencies in higher visual areas mentioned in Chapter 2. The areas in the primary visual cortex that we consider are V1, V2, V3, VP, V3A and V4v. These areas are considered the most prominent early visual areas and can be located with retinotopic mapping (Sereno *et al.*, 1995; Warnking *et al.*, 2002). The higher visual areas selected are V4, LOC, PPA, FFA, hMT+ and FEF. FEF and V4 were selected because they show remarkably early and late single cell recording responses respectively, which in turn could be explained by (a lack of) direct

connections to subcortical structures. The other areas were selected because they are considered essential areas for visual recognition of complex scenes.

If we manage to reliably localize all the areas mentioned above, we will obtain regions-of-interest (ROIs) that may serve as the starting point to ascertain the structural, functional and effective connectivity in the human visual system.

Methods

Participants:

Five healthy subjects (all male, all righthanded, age range 24 - 28) participated in this experiment. All subjects had normal or corrected-to-normal vision and gave informed written consent.

Stimulus presentation & task design:

All stimuli were presented binocularly with a video projector on a frosted projection screen at the back of the scanner tunnel. A mirror system was used so that the subject could see the images projected on the screen. All stimuli were generated and/or presented with custom written software (StimulDX) using the Microsoft Windows DirectX graphics library. The task given to the subject was to fixate and attentively follow the visual stimulation, unless instructed otherwise.

Early visual areas

The responsiveness and delineation of early visual areas was investigated with retinotopic mapping (Sereno *et al.*, 1995; Warnking *et al.*, 2002). Conventional black and white contrast reversing (8 Hz) checkerboard rings and wedges were used for eccentricity and polar angle mapping respectively. The eccentricity ring started with a radius of 1° visual angle and expanded to 12° within 96 seconds. For polar angle mapping, the wedge was 22.5° visual angle. The wedge started at the left horizontal meridian and rotated a clockwise full cycle in 96 seconds. Each retinotopic mapping experiment consisted of eight repetitions of expansion and rotation respectively.

LGN and SC

Recent work has shown that the subcortical structures LGN and SC can be functionally localized (Kastner *et al.*, 2004; O'Connor *et al.*, 2002; Schneider and Kastner, 2005; Schneider *et al.*, 2004). Generally speaking all these authors used a modified version of the retinotopic mapping procedure. The procedure used here was the same as described above albeit with different width and movement speed of the stimuli. The ring for eccentricity mapping had double the width and expanded in 48 seconds. For polar angle mapping, the wedge was 67.5° visual

angle and a full cycle rotation lasted 48 seconds. In this case each retinotopic mapping experiment consisted of 13 expansions or rotations.

Pulvinar

The localization by functional means of the Pulvinar has also recently been discussed in the literature (Kastner *et al.*, 2004). Kastner and colleagues used the type of stimuli described above to elucidate a response in the LGN and SC, but added a task instruction that was aimed at having the subjects covertly direct attention. Subjects were instructed to direct their attention, but not their gaze, at randomly occurring luminance changes along an arc at 10^0 eccentricity. Because luminance changes in a black and white checkerboard are hard to detect we used a modified version of a different task from Brefczynski and DeYoe (1999), also designed to have a subject covertly directing attention. In a block design the subject was presented with two stationary wedges with black and white contrast reversing (8 Hz) checkerboard patterns, at the left and right horizontal meridian. In the middle was a fixation point. During the covert attention shift condition, an arc of the checkerboard at a semi-random location in the wedges would flash dark blue. The subjects were asked to direct their attention toward that arc, without taking their gaze from the fixation point. During the other condition subjects were asked only to fixate. All subject briefly practiced this outside of the scanner before the experiment.

PPA, FFA and LOC

The areas PPA, FFA and LOC were identified in a single run by showing buildings, faces, objects and scrambled objects. The images shown were black and white digital photographs. Pictures of scrambled objects were created by tessellating object images into square sections of 10 x 10 pixels and then randomizing the location of those squares in a concentric ring around the location of the original image. The images were in a block design alternating stimulation of 13 seconds interleaved with fixation periods of 16 seconds. In each block a particular kind of stimulus was presented. Each block was repeated 6 times. Within each block stimuli were flashed for 666 ms with 17 ms fixation in between. These procedures are a modified version of what other authors used to localize these areas (Epstein *et al.*, 1999; Epstein and Kanwisher, 1998; Kanwisher *et al.*, 1997; Malach *et al.*, 1995). Area LOC was localized by contrasting the object condition vs. the scrambled objects condition, the area PPA by contrasting the houses condition with the faces condition and the area FFA by contrasting the faces condition with the objects condition.

hMT+

The area hMT+ was identified by contrasting the hemodynamic response of the brain during presentation of moving dots with a control stimulus consisting of

stationary dots. The moving dots, or flowfield, consisted of 400 white dots (dot size: 0.06×0.06^0 , dot velocity $3.6 - 14.4^0/s$) moving radially outward on a black background (Tootell *et al.*, 1995). The block design consisted of 4 blocks in the moving condition and 4 blocks in the stationary condition, interleaved with fixation. Both blocks and fixation lasted 15 seconds.

V4

The main human color centre, V4 was identified with a modified version of the task used by McKeefry and Zeki (1997). V4 was identified by contrasting the hemodynamic response during the presentation of chromatic images with the response during the presentation of achromatic images. The chromatic images consist of Mondrian patterns made of eight differently colored elements, assembled in such a way as to provide an abstract scene with no recognizable objects. The chromatic condition consisted of this colored pattern being alternated at 1 Hz with a scrambled version of the same pattern. During the achromatic condition the same patterns were shown at the same rate but the colors in the images were converted to different tones of grey, while maintaining isoluminance. Maintaining isoluminance means changing color while maintaining the total luminance of the image. Both the chromatic condition and the achromatic condition were repeated in 7 blocks and all blocks were interleaved with blocks of rest. All blocks lasted 16 seconds. A fixation cross was visible in the foreground during all conditions.

FEF

The visual stimuli and task designed to elicit a hemodynamic response in the area FEF is also based on earlier work, albeit more loosely. In a review of the literature Munoz and Everling (2004) state that the FEF has a crucial role in executing voluntary saccades. Several authors show that there is a strong hemodynamic response in this area during voluntary saccades and pursuit eye-movement (Connolly *et al.*, 2002; Petit *et al.*, 1997; Petit *et al.*, 1999). However, these authors also report simultaneous activity in the IPS during these tasks. By using the anatomical part of the neurophysiological definition of FEF (the caudalmost portion of the frontal convexity) by Paus (1996) we can exclude the activity in the IPS. We used a simplified version of the tasks used by the authors mentioned above. In a block design subjects were asked to direct their gaze to white circles appearing at an interval of 2 Hz at semi-random locations on the horizontal and vertical meridian. During both rest and saccade conditions a white fixation cross was visible. When there were no circles on the screen, subjects were asked to rest their gaze on the cross. There were 10 blocks of 16 seconds in the saccade condition, interlaced with rest periods of equal length.

Image acquisition:

Imaging was performed on a 3 Tesla head scanner (Magnetom Allegra, Siemens medical Systems, Erlangen, Germany) located at the M-BIC institute in Maastricht, The Netherlands. The scanner was equipped with a standard quadrature birdcage head coil.

Anatomical measurements were obtained once each session in the form of a three-dimensional T1-weighted data set encompassing the whole brain. For precise anatomical reference, a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence was used. The scan parameters were: repetition time [TR] = 2250 ms, echo time [TE] = 2.6 ms, flip angle [FA] = 9^0 . There were 192 slices each with a field of view [FOV] of $256 \times 256 \text{ mm}^2$, matrix size = 256×256 , slice thickness = 1 mm, no gap, which leads to a voxel size of 1 mm^3 .

Functional measurements for the *subcortical areas* were acquired with a T2* weighted echo planar sequence, with the following scan parameters: [TR] = 2000 ms, echo time [TE] = 35 ms, flip angle [FA] = 90^0 , field of view [FOV] = $225 \times 225 \text{ mm}^2$, matrix size = 128×128 , number of slices = 24, slice thickness = 2 mm. The effective voxel resolution therefore was $1,75 \times 1,75 \times 2 \text{ mm}$. Functional measurements for the *early visual areas* were done with the following scan parameters: [TR] = 2000 ms, echo time [TE] = 30 ms, flip angle [FA] = 90^0 , field of view [FOV] = $224 \times 224 \text{ mm}^2$, matrix size = 64×64 , number of slices = 32, slice thickness = 2 mm. Effective voxel resolution = 2 mm^3 . Functional measurements for the *higher visual areas* were done with the same scan parameters only slice thickness was different (3,5 mm) to facilitate whole brain scanning.

Image analysis:

Functional and anatomical images were analyzed using BrainVoyager QX (version 1.8; Brain Innovation, Maastricht, The Netherlands, see Goebel *et al.*, 2006). Localizing the different modules required different kinds of analysis. The end results were always localized regions in original space in individual subjects.

The time courses of activation of individual voxels were constructed from the functional images and corrected for the temporal difference in acquisition of different slices using sinc interpolation (slice scan time correction). Small interscan head movements were corrected for by a rigid body algorithm rotating and translating each functional volume in 3D space. To exclude scanner-related signal drifts, a linear trend removal was performed. Temporal high-pass filtering was applied to remove temporal frequencies lower than 3 cycles per run. Voxel time courses were then coregistered to the structural volume in original space

using trilinear interpolation. No spatial or temporal smoothing was applied to the functional time courses.

Higher visual areas and the pulvinar

Subsequently, the functional data for the higher visual areas and the pulvinar data were analyzed using multiple regression models consisting of predictors, which corresponded to the particular experimental conditions of each experiment. Following Boynton *et al* (1996), the predictor time courses were constructed as box-car functions and filtered through a linear model of the BOLD response. To compare the BOLD responses during experimental conditions, general linear model (GLM) contrasts were computed resulting in t-maps. In all higher visual areas, signal differences with threshold of $p < 0.0001$ were considered significant. Because of the deep location and small size of the expected pulvinar activation, the threshold for localizing this structure was lowered to $p < 0.05$. Thresholds were one-tailed.

Early visual areas and the LGN and SC

The early visual areas and the LGN and SC were localized using the retinotopic mapping data using cross correlation analysis (for details, see Goebel *et al.*, 2001; Linden *et al.*, 1999). The retinotopy of the early visual areas has long since been established but only recently has it been shown that the LGN and SC are also organized retinotopically (Kastner *et al.*, 2004; O'Connor *et al.*, 2002; Schneider and Kastner, 2005; Schneider *et al.*, 2004). The eccentricity and polar angle represented by a given voxel were determined by finding the lag value maximizing the cross-correlation. The obtained lag values at each voxel, corresponding to the eccentricity or polar angle of optimal stimulation, were encoded in pseudocolors. To be able to localize the subcortical structures at lower cross-correlation thresholds a cluster threshold of 30 voxels was used. In order to delineate the boundaries of the early visual areas V1, V2, V3, VP, V3A and V4v on a flat representation of the anatomical data, additional processing was necessary. The cortical surface was reconstructed, inflated and flattened and the retinotopic maps were superimposed on those surfaces. The delineation of the areas was based on the polar angle mapping results but when the delineation was not clear cut visual field sign mapping (Sereno *et al.*, 1994) was used.

Results

Because of lateral functional specialization, attentional differences between subjects, scanner noise or other confounds, not all areas were found in all subjects. Table 1 shows the areas localized for each subject and the total number of successfully localized areas.

Table 2 shows the results of the GLM analysis of the higher visual areas FEF, FFA, hMT+, LOC, PPA and V4. The contrast, in averaged percent BOLD signal change, between the condition in which a particular area is active, is plotted against its contrasting condition, either rest or a different active condition, for all areas in all subjects (for exact contrast see Methods, Task Design). The numbers used consistently refer to the same subjects in all tables and figures.

Figure 1 shows the results of the retinotopic delineation of the early visual areas in one hemisphere in one representative subject. In figure 1A a retinotopic polar map of one hemisphere is super imposed on the reconstructed, inflated and flattened cortex. Colors represent the polar angle to which that part of the visual cortex is most sensitive. In figure 1B the localized areas are shown, visualized on the same flattened surface.

Figure 1: A) The retinotopic polar map of the left hemisphere is super imposed on the reconstructed, inflated, cut (anatomical cut) and flattened cortex. Dark grey represents concave cortex surface folding, light grey represents convex surfaces. Colors represent the polar angle of the stimulus. SMP smoothing applied to the data. B) The areas delineated with the help of the polar map in A and a visual field sign map, visualized on the same flattened surface.

Figure 2 shows the results of the functional localization of the subcortical areas LGN, SC and pulvinar. Because the LGN and SC were localized with retinotopic mapping, the retinotopic organization of the LGN and SC can also be discerned in this figure. What is marked as inferior pulvinar might overlap with the LGN or be LGN activity only.

Figure 3 shows the end results of all these analyses. All localized areas can be seen in 3D space in all individual subjects, color coded per area. In figure 3A the transversal viewpoint has been chosen so all areas can be viewed from above, and

in 3B the viewpoint has been set to somewhere in between transversal and sagittal. With these combined viewpoints all areas can be seen. As an anatomical reference the anatomical data are also shown, in sagittal, coronal and transversal cut.

Area Acronym:	Left Hemisphere						Right Hemisphere					
	1	2	3	4	5	Tot	1	2	3	4	5	Tot
LGN	1	1	0	1	1	4	1	1	0	1	1	4
SC	1	1	0	1	1	4	1	1	0	1	1	4
PUL	0	0	0	1	0	1	1	0	0	0	0	1
V1	1	1	1	1	1	5	1	1	1	1	1	5
V2	1	1	1	1	1	5	1	1	1	1	1	5
V3	1	1	1	1	1	5	1	1	1	1	1	4
VP	1	1	1	1	1	5	1	1	1	1	1	4
V3A	1	0	1	1	1	4	1	0	1	1	1	4
V4v	1	1	1	1	1	5	1	1	1	1	1	5
FEF	1	1	1	1	1	5	1	1	1	1	1	5
FFA	0	1	1	0	0	2	1	1	1	1	1	5
hMT+	1	1	1	1	1	5	1	1	1	1	1	5
LOC	1	1	1	1	1	5	1	1	1	1	1	5
PPA	1	1	1	1	1	5	1	1	1	1	1	5
V4	1	0	1	0	0	2	1	1	0	0	0	2
Total number of subjects: 5 (All were right handed)												

Table 1: The number of successfully localized areas. Each cell in the table represents an individual area that could have been localized. All areas and all subjects are in the table. Localized areas are marked with the number one and a grey color and areas that were not found are marked with the number zero and the cell is left white.

Table 2: Event related averages for the areas FEF, FFA, hMT+, LOC, PPA and V4 for all individual subjects for the left and the right hemispheres. The x-axis plots the time course in scans, the y-axis plots the fMRI response in percent BOLD signal change. An empty cell in the table means that that particular area could not be localized.

Figure 2: Clockwise: localization of left LGN, left SC, Inferior Pulvinar and Superior Pulvinar. Surrounding activation suppressed for clarity. All Images from subject 1, except superior pulvinar which is from subject 4. Left and right are mirrored according to radiological conventions. For image analysis details see Methods, Image Analysis section.

Figure 3A: All localized areas seen in 3D space in individual subjects (denoted with numbers also found in table 1 and 2) from a superior viewpoint. A transversal slice of the anatomical data has been added below for reference. Functional and anatomical data are not rotated to ACPC space nor transformed to TAL space (data is in 'original space').

Figure 3B: All localized areas seen in 3D space in individual subjects (denoted with numbers also found in table 1 and 2) from a left lateral and slightly superior oblique viewpoint in order to view as much areas as possible with as many as possible anatomical landmarks also visible. Transversal, coronal and saggital slices of the anatomical data have been added for reference. Functional and anatomical data are not rotated to ACPC space nor transformed to TAL space (data is in 'original space')

Discussion

We have shown that it is possible to localize many areas of the visual system in one session in the MR-scanner even if these areas are from several different subsystems of the visual system, requiring different task designs and image analysis techniques. Multiple areas were identified with more uniform methods (e.g. exact same thresholds for all higher visual areas) then would have been the case when these areas would have been localized over multiple studies. We were able to localize subcortical, primary visual and higher visual areas in original space in single subjects, successfully mapping a large part of the functional structure of the visual system.

Subcortical areas

The work shown here is one of the few reproductions of the results of Schneider, Richter *et al* (2004), Schneider and Kastner (2005) and Kastner, O'Connor *et al* (2004) showing the retinotopic organization of the LGN and the SC and the functional localization of the pulvinar respectively (See Figure 2). Due to the difficulty of localizing such a small and relatively deep brain structure, not all subcortical structures were found in all subjects (See Table 2).

Pulvinar

Localization of the pulvinar proved to be particularly difficult. Although the pulvinar is a relatively large structure, activity could only be seen in parts of this structure, near the fornix; this is similar to the results found in the original paper (Kastner *et al.*, 2004, see Figure 7 in the original publication). Like all subcortical structures, the pulvinar is close to a ventricle, and therefore a misaligned ventricle artifact might be mistaken for activity in these structures. Small misalignments can never be fully excluded in MRI results, as functional EPI images always have non-linear distortions compared to the anatomical images on which they are overlaid (Jezzard *et al.*, 1999). Because subcortical structures are small and always close to a ventricle, localizing these structures might benefit especially from EPI image distortion correction (Hutton *et al.*, 2002; Jezzard and Clare, 1999). The question is also why an area that constitutes a quarter of the total mass of the thalamus, and is highly interconnected, shows so little activation. Strikingly, the activity was consistently in the same location, a more superior and a more inferior location (see figure 2). This can be explained by the fact that the pulvinar is divided into several sub-regions, of which only the superior and inferior parts are visual (Grieve *et al.*, 2000). However, care should be taken when interpreting activity in the inferior Pulvinar as the LGN is close by and activity could be overlapping. Therefore, the Pulvinar was not considered 'localized' when there was only activity in the inferior Pulvinar. In the work by Kastner and O'Conner (2004) we can see that the inferior part of the Pulvinar is always active

during visual stimulation, but the superior part is only active during covert attention shift. This supports the view that the pulvinar is organized from lower (less complex) in the inferior part to higher (more complex) in the superior part (Grieve *et al.*, 2000).

LGN

The LGN on the other hand, proved relatively easy to localize with retinotopic stimulation and the retinotopic organization is quite apparent in the results (See Figure 2). However, the activation in the left pulvinar had more volume (quantified by the amount of active voxels) than the activity in the right LGN in 3 of the 4 subjects in which both LGN's were localized. This is remarkable as it is quite normal for higher visual areas to show lateral specialization but is not expected in a structure that is only involved in low level vision. This might be due to the fact that there are huge amounts of feedback projections to LGN from the early visual areas (Sherman *et al.*, 1998).

Localizing subcortical areas with a saccade task

To sum up, the complete set of subcortical visual areas was found, but required increasing the statistical threshold, which in turn necessitated the use of a cluster threshold. Finding the Pulvinar in all subjects remained problematic. As mentioned above, this could be caused by the small volume of the sub-cortical areas, making them more prone to alignment problems. Other possible causes could be signal loss due to its deep location in the brain, a weaker hemodynamic response in subcortical areas or different neurovascular coupling in these areas.

In principle the subcortical areas studied are always active during visual stimulation of the subject. Therefore, in an attempt to find a better localizer than the mediocre results mentioned above, all other conditions were also checked for activation in the subcortical areas. Remarkably the LGN, SC and Pulvinar are all clearly visible during presentation of the stimuli designed to elucidate a response in the FEF and this was apparent even without lowering the threshold (See figure 4). LGN and SC are clearly visible and the SC has more active voxels. Even the superior Pulvinar is consistently localized. This effect was only apparent during the FEF localizer and not during presentation of the other visual stimuli like the 'broad visual stimulation' used as localizer for PPA, FFA and LOC. If these successful extra subcortical localizations are compared with the earlier total localization results (table 3), it is apparent that this way of localizing subcortical areas can not only match the earlier results but also improve on them by localizing an additional ten individual areas. The locations of the 'planned' subcortical localizer and the 'saccadic' subcortical localizer were remarkably similar, which seems to indicate both localizers are activating the same areas only with different intensities. Also, the results of the 'saccadic' subcortical localizer were noticeably

less noisy, enabling the use of lower threshold values (mostly $p < 0,0001$ instead of $p < 0,05$). In a review of the literature, the LGN, the SC and the Pulvinar (thalamus) are all mentioned as part of neural circuitry controlling saccadic eye movement (Munoz and Everling, 2004), and this might explain why they are active during the saccade task, but not during the other tasks/conditions.

Area Acronym:		Left Hemisphere						Right Hemisphere					
		1	2	3	4	5	Tot	1	2	3	4	5	Tot
Original localizer	LGN	1	1	0	1	1	4	1	1	0	1	1	4
	SC	1	1	0	1	1	4	1	1	0	1	1	4
	Pul	0	0	0	1	0	1	1	0	0	0	0	1
Saccadic Localizer	LGN	1	1	1	1	1	5	1	1	1	1	1	5
	SC	1	1	0	1	0	3	1	1	1	1	1	5
	Pul	1	1	1	1	1	5	1	1	1	1	1	5

Table 3: Comparing the number of successfully localized areas between the ‘original’ sub-cortical localizers (top) and the ‘saccadic’ localizer (bottom). Localized areas are marked with the number one and a grey color and areas that were not found are marked with the number zero and the cell is left white. Lay-out is the same as table 1

Figure 4: Activation in the subcortical structures during the FEF localizer (see Methods, Stimulus Presentation section). The superior Pulvinar, the LGN and the SC can be clearly seen in both hemispheres. The activation denoted as LGN might also be inferior Pulvinar or both. While the statistical threshold had to be lowered to localize the deep brain structures in our original results, there was no need to lower them while looking for these structures functionally while using the FEF localizer (the threshold here is $p < 0.0001$, which was the standard in all the localizers used).

In retrospect one might conclude that although the retinotopic stimuli used to localize subcortical structures are capable of detecting the retinotopic organization of the subcortical structures, a saccade task is unexpectedly much more suited to reliably and efficiently functionally localize the LGN, the SC and the Pulvinar. Therefore we suggest using a saccade task as a replacement or complement for mapping subcortical visual structures if the location and/or volume of the subcortical area is important and retinotopic organization is not.

Primary visual areas

The localization of the areas in the primary visual cortex was successful (See Figure 1 and 3). Only the visual areas V3A proved hard to find in one case. Although the localization of the early visual areas as a whole can be reliably estimated from the retinotopic data, the delineation of areas within this whole is to some degree subjective, especially for bordering areas (e.g. V1 and V2 or V2 and V3), due to the nature of the technique, and more specifically due to its lack of absolute ways to draw borders between areas. Because we were able to reliably obtain both polar angle and eccentricity gradients we were able to analyze the retinotopic data using visual field sign mapping. Field sign mapping provides a more objective method for delineation areas in the primary visual cortex (Sereni *et al.*, 1994) but this technique has seen infrequent use in recent literature. Visual field sign mapping has been used in the present study when the location of borders between areas were ambiguous (e.g. when they could be drawn in multiple locations). In our experience field sign mapping is a valuable tool in difficult cases, but noisy or patchy data drastically reduce its objectivity. The amount of smoothing used can influence results in some cases. Also, field sign mapping tends to lead to a very conservative estimation of the total extent of (an area in) the visual cortex, because a particular patch on the cortical map has to be sensitive to both eccentricity and visual angle for it to be considered part of the early visual cortex. The analyses mentioned call for some prudence when using these results for connectivity analyses. The delineation problems could be especially troublesome when trying to analyze connectivity between early visual areas. The conservative estimation of the extent of early visual areas can be seen as both a blessing and a curse. On the one hand this possible underestimation could prove troublesome when trying to quantitatively compare the amount of connectivity between areas (either within the primary visual cortex or between areas outside and inside of the primary visual cortex). On the other hand, the reason for this conservative estimation of the extent of areas, the use of both eccentricity and polar angle gradients, increases the reliability of the localizations because the centre of an area is more likely to be included. This would be an advantage when using this data set as starting point for further connectivity analyses and could be further enhanced by ‘shrinking’ the areas before using them as seed points. This

might also lessen the delineation problem when looking at connectivity between early visual areas.

Higher visual areas

The relatively straightforward localization of the higher visual areas was also successful; all areas, except V4, were found at least unilaterally in all subjects (See Table 2). Only FFA and V4 were not always found. The left FFA was not always found but this is to be expected as the FFA is known to be strongly lateralized (all the subjects were right handed). Area V4 turned out to be harder to localize than expected, and this could not be attributed to an effect of lateralization. To localize V4 a relatively long task design was required and even then the total extent of activation was far less than in the publication from which the task design originated (McKeefry and Zeki, 1997). In this publication the authors go to great lengths to minimize the amount of flicker between different stimuli and set individual isoluminance values, whereas we induced flickering (aiming for a stronger BOLD response) and the isoluminance was only calculated on the RGB level for all subjects. These differences may account for the differences in activation of V4 between the publications. Also, the area that was active during the saccade task was consistently larger than 'FEF proper' as defined by Paus (1996). This is also apparent in other literature (Connolly *et al.*, 2002; Petit *et al.*, 1997; Petit and Haxby, 1999) and is probably caused by the use of a saccade task instead of a smooth pursuit task (Petit and Haxby, 1999, see Figure 3 in the original publication).

Conclusion

We have shown that it is possible to localize subcortical, early-visual and higher-visual areas in the visual system (except for V4), in original space, in single subjects, in a single session, even if this requires different analysis techniques. This has the benefits of unified parameters and conditions for all areas and consistency in location within a single subject. Some clear advice can be given about these kinds of localizers. First, if subcortical visual structures need to be localized, a 'saccadic localizer' is very effective and efficient. Second, when designing stimuli for a V4 localizer, determining the amount of flicker and isoluminance might be critical. Third, the functional definition of FEF, and thus task design, strongly influences the extent of the localization of FEF. Lastly, if these kinds of localizers are used for further analysis, care needs to be taken when interpreting connections to or from individual areas within the primary visual cortex, because the boundaries of these areas are not clear-cut due to the limitations of retinotopic mapping. In conclusion, a large part of the functional structure of the visual system has been effectively mapped. This can be especially beneficial for structural, functional or effective connectivity analyses. We will use

this mapping to examine the structural connectivity in the visual system with DTI in the next chapter.

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Chapter 4

Exploring Subcortical - Cortical Connections in the Human Visual System using Diffusion Tensor Tractography Reveals Direct Routes to Higher Visual Areas

This chapter is based on:

Capalbo, M., Roebroek, A., Jeurissen, D., and Goebel, R. (2008). Mapping the Large-scale connectivity of the Visual System with DTI tractography. In preparation

Abstract

For our understanding of the visual system it is essential to know how the areas in the visual system are connected. However, due to the limitations of classical structural connectivity techniques, the structural connectivity of the human visual system remains largely unknown. To study the structural connectivity of the human visual system Diffusion Tensor Imaging (DTI) was combined with fiber tractography, using functionally localized Volumes Of Interest (VOIs) as seed and target regions. Because recent results from patients with cortical lesions suggest that routes from the subcortical structures directly to the cortex play a more important role than previously thought, these connections were the focus of this study. Despite the limitations of the technique, tracts between the subcortical areas, and from the subcortical areas to the early visual areas, were reliably localized. Tracts between the subcortical areas and FEF, PPA and FFA were found relatively often. Tracts from the Superior Colliculus (SC) were found to connect to relatively few cortical areas. The differences and similarities between the revealed connections in humans and those described for the macaque are discussed.

Introduction

When trying to explain how a system works it is generally useful to know what the elements of the system are and how these elements are connected. This is especially true for complex biological systems like the brain. To truly understand the function of the brain as a whole, it is essential to know how cooperative brain regions are connected. Knowing where a certain area's input comes from and where its output might go, might be an essential hint to the exact functioning of that area (1994). Traditional models of the connectivity of the brain (e.g. Andersen *et al.*, 1990; Felleman and Van Essen, 1991; Zeki and Shipp, 1988), often ignore subcortical structures (Mountcastle, 1998). These structures are also referred to as thalamic or deep-brain structures. The omission of subcortical structures from most connectivity models might be because their function is considered clear, or their connectivity pattern known. However, the function of these subcortical structures is still not clear (e.g. Carandini *et al.*, 2005; Koch, 2004a) and their connectivity pattern is far more complex than these models assume. For instance, in the popular hierarchical model (Felleman and Van Essen, 1991) there is a simple serial connection from the retina to the Lateral Geniculate Nucleus (LGN) to V1, other thalamic structures are omitted and although in later publications some thalamic structures are added, none of these structures are connected to higher visual areas. However, these subcortical to cortical connections are known to exist in the monkey visual system. The monkey visual system resembles the human visual system but unlike the human visual system we have been able to study its structural connectivity for decades with tract tracing

studies. This large body of structural connectivity data has been collated in the Cocomac database (Stephan *et al.*, 2001). If we query this database and integrate the data from multiple studies and parcellation schemes (with the help of a technique called ORT, see K. E. Stephan *et al.*, 2000) we can not only see that the connectivity pattern between thalamic structures is more complex than a simple serial scheme, there is also a large number of connections from the thalamic structures to higher visual areas, in effect bypassing the primary visual cortex (see table 1). Table 1 shows that the Pulvinar (PUL) is connected to multiple early and higher visual areas and that this is not the case for the Superior Colliculus (SC) which is only connected to primary visual cortex (V1).

	LGN	PUL	SC
LGN			
PUL	1		
SC	1	1	
V1	1	1	1
V2	1	1	0
V3	0	1	0
V3a			
V4v	0	0	
VP	0	0	0
FEF	0	1	
MT	0	1	
V4	0	1	
PPA			
FFA			
LOC			

Table 1: Integrated resulting projections from the subcortical structures Lateral Geniculate Nucleus (LGN), the Superior Colliculus (SC) and the Pulvinar (PUL) to the areas in the Felleman and Van Essen (1991) parcellation scheme (acronym: FV91) from the Cocomac database (Kotter, 2004; Stephan *et al.*, 2001). Only the target areas under consideration in this paper are shown. Areas not found in Macaque (PPA, FFA, LOC) were added because they are under consideration in this paper. A zero as table entry means no connection has been found, a one means a connection has been found and an empty entry means that no study in the Cocomac database has information on this connection.

Including these subcortical to cortical connections in the connectivity of the visual system might explain some intriguing results in single cell recording, modeling, structural connectivity and lesion studies. In single cell latency studies in macaque, massive simultaneous activity has been observed in areas that are very different in their supposed path length from the retina (Lamme and Roelfsema, 2000; Nowak and Bullier, 1998; Schmolesky *et al.*, 1998). A data driven modeling study has shown that a model that incorporates routes from subcortical structures direct to cortical areas can explain this simultaneous activity whereas a model that does not have these connections can not (Chapter 2). These subcortical routes could also explain recent human lesion studies. Lesion studies on human hemianoptic or blindsight patients has taught us that despite unilateral lesions in early visual areas, activity in higher visual areas in the damaged hemisphere resembles the activity found in the undamaged hemispheres (Goebel *et al.*, 2001; Schoenfeld *et al.*, 2002). Also, the activity in higher visual areas precedes activity

in the undamaged part of the lower visual areas (Hinrichs *et al.*, 2006). How can areas higher ‘upstream’ in the system be activated in an almost normal way when almost all of their input from lower levels has been destroyed? Direct subcortical to cortical connections might help to explain some or all of these results.

It would be interesting to see if these connections actually exist in the human brain. However, the possibility to study connectivity between distinct areas in the human brain is restricted due to the limitations in current anatomical labeling techniques (Kim *et al.*, 2006). Invasive tract tracing studies can only be done in humans *post mortem* and then only for distances of tens of millimeters, longer distance connections outside of the major tracts can only be studied in a small number of informative patients with lesions (Behrens *et al.*, 2003). The solution is a technique that can study structural connectivity in the human brain in-vivo. Despite its limitations, the only technique to date that is capable of revealing structural connectivity in the human brain is Diffusion Tensor Imaging (DTI) in combination with fiber tractography. By utilizing the fact that water diffusion is greater along the direction of axon-bundles than perpendicular to it, DTI can be used to visualize the micro structure of white-matter fiber-bundles (e.g. Le Bihan, 2003; Le Bihan *et al.*, 2001). By applying a line propagation algorithm to this kind of data, large white-matter fiber-bundles can be reliably traced from area to area (Basser *et al.*, 2000; Conturo *et al.*, 1999; Mori *et al.*, 1999).

Because of the considerations mentioned above, the goal of this study is to investigate the structural connectivity between thalamic areas and cortical areas of the human visual system in-vivo using diffusion tensor tractography.

Methods

Localizing thalamic and cortical areas

To study the connectivity between brain areas, the first necessity is a method to localize these areas. An fMRI study done by us earlier to reveal the large-scale functional structure of the visual system (Chapter 3) provided the Volumes Of Interest (VOIs) used as starting points for the connectivity analysis in the present study. Subcortical, primary visual and higher visual areas were localized. The Lateral Geniculate Nucleus (LGN), the Superior Colliculus (SC) and the Pulvinar (PV) were the subcortical areas chosen, because of their possible role in explaining massively simultaneous timing data (Chapter 2). The primary visual areas localized were V1, V2, V3, VP, V3A and V4v. The higher visual areas FEF and V4 were included because they show remarkably early and late latencies, respectively, in single cell latency studies (Lamme and Roelfsema, 2000; Nowak and Bullier, 1998; Schmolesky *et al.*, 1998). The other higher visual areas that were selected, besides FEF and V4, were LOC, PPA, FFA, hMT+. These areas

were chosen because of their role in high level visual perception. In general, areas were chosen that are known to be localizable with standard experimental paradigms, and would contribute to an adequate sampling of the large-scale structure of the visual system.

The areas were localized functionally with a wide range of stimuli designed to elicit a response in the desired areas with respect to baseline and if necessary, an adequate control response for subtraction. Functional measurements were all acquired with a T2* weighted echo planar sequence. For optimal spatial resolution, the resulting data from the thalamic and early visual localizers was recorded with a resolution of $2 \times 2 \times 2 \text{ mm}^3$. To be able to cover the whole brain (within 2 seconds) the resolution of the sequence used to localize the higher visual areas was $3,5 \times 3,5 \times 3,5 \text{ mm}^3$. For precise anatomical reference, the structural images were acquired with a T1-weighted MPRAGE sequence with $1 \times 1 \times 1 \text{ mm}^3$ resolution. All scans were performed in a 3 Tesla Siemens head scanner (Magnetom Allegra, Siemens medical Systems, Erlangen, Germany),

Functional and anatomical images were analyzed using BrainVoyager QX (version 1.8; Brain Innovation, Maastricht, The Netherlands, see Goebel *et al.*, 2006). The images from the localizers for the early visual areas were analyzed with retinotopic mapping techniques (Sereni *et al.*, 1995; Warnking *et al.*, 2002), the location of the higher cortical areas was inferred by applying the General Linear Model (GLM) statistics to the BOLD data, and the thalamic areas were identified by a combination of these methods. All resulting regions of interest were transformed back to the original resolution of the brains of the individual subjects.

For more details concerning area inclusion criteria, stimuli, data acquisition and analysis see chapter 3.

Diffusion Tensor Imaging

Imaging was performed on a 3 Tesla head scanner (Magnetom Allegra, Siemens medical Systems, Erlangen, Germany) provided with standard a quadrature birdcage head coil, located at the M-BIC institute in Maastricht, The Netherlands. Diffusion weighted MR-images were acquired using a doubly refocused spin-echo echo-planar imaging (SE-EPI) sequence. (TR/TE = 9800ms/82ms). 108 directions of gradient-encoded diffusion weighted images were acquired with $b = 1000 \text{ s/mm}^2$. Ten reference images with no diffusion weighting were also acquired. The resolution was $2 \times 2 \times 2 \text{ mm}^3$. Because the VOIs are in original space, no spatial rotations or scale resizing of the imaging data was necessary.

Diffusion Tensor Model and Fiber Tracking

All processing and visualization was performed in a custom-written C++ software package called TrackMark developed by author AR using the OpenGL graphics library for 3-D visualization.

In the diffusion tensor model, each voxel contains a diffusion tensor (DT) that models the diffusion profile as a 3D Gaussian with three orthogonal axes or eigenvectors of diffusion (Basser *et al.*, 1994). This diffusion tensor can be geometrically represented as an ellipsoid. To estimate the diffusion tensor model voxel-wise singular value decomposition was used (Press *et al.*, 2002). To obtain the three eigenvectors each tensor was diagonalized by Jacobi rotations. Estimated tensors were visualized as either cylinders whose length represented the primary eigenvector and the direction represented the direction of that vector or ‘boxoids’ whose form represent all three eigenvectors and are color coded for direction (Pajevic *et al.*, 1999). Maps of fractional anisotropy (Pierpaoli *et al.*, 1996) could be shown in the same space as the tensors for reference. Anisotropy is essentially a measure of the amount of variance present in the three eigenvalues of the diffusion tensor. The maps provide a way to visualize the general amount of diffusion within a given area and provide a stopping criterion for the tracking algorithm. The structural MRI maps could also be overlaid for reference.

Fiber tracking can be done with streamline or line propagation algorithms by following the local estimated primary eigenvectors from a seed point. This works well in regions where a single coherent track is present, but does not work so well in more complex situations, such as crossings, in these situations using full local tensor information yields better results. We used fourth order Runge-Kutta method (Press *et al.*, 2002) as a stable and accurate way to advance the tract line with a stepsize of 0,5 mm. Local tensors for this method were computed from the discrete tensor volumes using tri-linear interpolation. Tracing was stopped either when the local FA was below 0,2 or when the angle between previous and current tracking direction was larger then 60 degrees. For further details see Roebroek *et al.* (2007).

Volumes of interest for tracking

The Volumes Of Interest (VOIs) used here were the VOIs from the previous chapter, chosen to adequately map the large-scale structure of the visual system and meant as the perfect starting point for a connectivity study such as this one. The VOIs for the subcortical areas were localized using a task involving saccadic eye movement as this task was found to yield much better results then the retinotopic tasks used in earlier studies (Chapter 3). The VOIs were converted to the resolution of the DT data (2x2x2 mm³). Each seed voxel was filled with 5x5x5 seed points as starting points for tractography.

Connections of interest

The total number of VOIs in one hemisphere of one subject is 15 (LGN, PUL, SC, V1, V2, V3, V3a, V4v, VP, FEF, hMT+, V4, PPA, FFA, LOC). This means there are 15 x 14 (excluding the connections-to-self) connections per hemisphere (See table 2). There are 5 subjects. The directionality in DT-tractography is not related to actual directionality in the brain, but being able to track a connection both ways yields more information about the connection and therefore it is useful to not only track a connection from A to B ('from-to') but also from B to A ('to-from'). All in all this means that there are 4200 possible connections (15 source areas x 14 target areas x 2 hemispheres x 2 directions x 5 subjects) excluding inter-hemispheric connections. To limit the search, only the connections that are relevant for our goal of exploring the subcortical-cortical connections, will be explored (these connections are grey in table 2).

Table 2: The matrix of the total amount of connections possible in the current data set. These can be divided in groups according to the type of area in which they originate and terminate, and these groups are marked with different patterns. To limit the amount of connections that have to be tracked, only connections to or from the subcortical areas will be studied. These connections are marked with a grey color.

Data reduction

The connection from A to B can also be tracked from B to A, in two hemispheres and in five subjects. All these connections provide information about the same connection and this allows us to reduce all this data into a single connection matrix for all subjects. To obtain these group results we must integrate all the results from individually tracked connections. Each individually tracked connection results in a number of tracked fibers from the source to the target. The first step is to dichotomize these results into 'connection found' (1), 'connection not found' (x). In some cases it was impossible to track a connection (-) due to lack of target or source VOIs. The process of collating all the different connection matrices into a single connections matrix is shown schematically in Figure 1.

Each step in the analysis leads to a matrix with percentages, each percentage representing the percentage of connections in which this particular connection was found. This percentage summarizes the data that is integrated in this particular step. If a connection could not be tracked because a target or seed VOI was missing, that connection was not included in the calculation of the average. The first step in Figure 1 is combining the connections in the left and right hemispheres into a single connectivity matrix. The second step is integrating the ‘from-to’ matrix with the ‘to-from’ matrix. If we visualize these matrices as 15 x 3 matrix and a 3 x 15 matrix, the integration can be conceptually visualized as transposing the 3 x 15 matrix and ‘adding’ the matrices. The third and final step consists of integrating the results over all subjects.

Results

Not all areas were functionally localized in all subjects in the dataset used (see Chapter 3). Table 3 summarizes, per subject, which areas were and which areas were not found. We can see that the SC and the area V3A were occasionally not found, FFA was sometimes not found in the left hemisphere due to lateralization and that V4 was often not found. When these areas were the target or source area of a tracking, the tracking was impossible. This leads to some ‘impossible to track connections’ (-) in the individual results.

Area Acronym:	Left Hemisphere					Right Hemisphere				
	1	2	3	4	5	1	2	3	4	5
LGN	1	1	1	1	1	1	1	1	1	1
SC	1	1	0	1	0	1	1	1	1	1
Pul	1	1	1	1	1	1	1	1	1	1
V1	1	1	1	1	1	1	1	1	1	1
V2	1	1	1	1	1	1	1	1	1	1
V3	1	1	1	1	1	1	1	1	1	1
VP	1	1	1	1	1	1	1	1	1	1
V3A	1	0	1	1	1	1	0	1	1	1
V4v	1	1	1	1	1	1	1	1	1	1
FEF	1	1	1	1	1	1	1	1	1	1
FFA	0	1	1	0	0	1	1	1	1	1
hMT+	1	1	1	1	1	1	1	1	1	1
LOC	1	1	1	1	1	1	1	1	1	1
PPA	1	1	1	1	1	1	1	1	1	1
V4	1	0	1	0	0	1	1	0	0	0

Table 3: The areas localized in the previous chapter. Successfully localized areas are marked with the number one and a grey color and areas that were not found are marked with the number zero and the cell is left white. For more details see Chapter 3.

1.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	100	100	
4 V1	100	50	0
5 V2	100	50	25
6 V3	100	25	25
7 V3a	100	0	25
8 V4v	25	25	0
9 VP	50	25	0
10 FEF	0	0	0
11 hMT+	0	0	0
12 V4	25	0	0
13 PPA	25	25	25
14 FFA	100	50	0
15 LOC	0	0	0

2.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	100	50	
4 V1	75	25	0
5 V2	100	0	0
6 V3	100	0	0
7 V3a	-	-	-
8 V4v	25	0	0
9 VP	50	0	0
10 FEF	75	50	25
11 hMT+	50	0	0
12 V4	0	0	0
13 PPA	25	50	0
14 FFA	75	25	25
15 LOC	25	0	0

3.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	0	0	
4 V1	100	50	0
5 V2	50	50	0
6 V3	75	50	0
7 V3a	100	100	0
8 V4v	75	0	0
9 VP	50	25	0
10 FEF	0	25	0
11 hMT+	25	25	0
12 V4	50	0	-
13 PPA	50	50	0
14 FFA	0	0	0
15 LOC	25	25	0

4.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	75	75	
4 V1	25	25	0
5 V2	50	25	0
6 V3	50	25	25
7 V3a	100	50	0
8 V4v	100	0	0
9 VP	0	0	0
10 FEF	25	50	50
11 hMT+	0	0	0
12 V4	-	-	-
13 PPA	0	0	0
14 FFA	0	0	0
15 LOC	25	0	0

5.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	100	100	
4 V1	100	0	0
5 V2	75	0	0
6 V3	75	25	0
7 V3a	100	25	0
8 V4v	100	50	0
9 VP	50	0	0
10 FEF	25	0	0
11 hMT+	25	0	0
12 V4	-	-	-
13 PPA	100	25	0
14 FFA	50	50	0
15 LOC	75	25	0

Table 4: The results of the DT-tracking per subject. Subject numbering is consistent with all other tables and figures in this and the previous chapter. The cell entries represent the percentage of connections where the tracking led to a connection between the two areas under investigation. The symbol '-' means that the connection was impossible to trace because the necessary areas were not localized.

Table 4.1 - 4.5 shows the tracking results per subject (after step 2 in the data reduction, see Methods). Subject numbering is consistent with all other tables and figures in this chapter and chapter 3 so that they can be compared. At first sight it is immediately apparent that large variations over subjects exist. Some trends can already be seen but a summary over all subjects is still needed. Table 5.1 is the resulting connection matrix after the third and last step in the data analysis, integrating the data over all subjects. To facilitate direct comparison, this matrix is the same size, and the areas are listed in the same order, as the monkey connectivity matrix in table 1.

In the group results in table 5.1 it is clear that some (groups of) cortical areas are more connected to subcortical areas than others. As a visual aide to identify these connections in the matrix, table 5.2 marks those parts of the matrix with numbers. Part I demonstrates that the LGN is highly connected to the early visual areas. In part II we can see that the subcortical areas are maximally connected. Part III shows evidence that FEF and the subcortical areas might be connected. In part IV seems to show that the areas PPA and FFA are connected directly to subcortical areas. Notably unconnected are the SC (part V), and the areas V4, hMT+ and LOC.

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	75	65	
4 V1	80	30	0
5 V2	75	25	5
6 V3	80	25	10
7 V3a	100	43,8	6,25
8 V4v	65	15	0
9 VP	40	10	0
10 FEF	25	25	15
11 hMT+	20	5	0
12 V4	25	0	0
13 PPA	40	30	5
14 FFA	45	25	5
15 LOC	30	10	0

	LGN	PUL	SC
1 LGN			
2 PUL	100		
3 SC	75	65	
4 V1	80	30	0
5 V2	75	25	5
6 V3	80	25	10
7 V3a	100	43,8	6,25
8 V4v	65	15	0
9 VP	40	10	0
10 FEF	25	25	15
11 hMT+	20	5	0
12 V4	25	0	0
13 PPA	40	30	5
14 FFA	45	25	5
15 LOC	30	10	0

Table 5: 1) The final connection matrix, integrating all individual tracked connections over all subjects, hemispheres and 'directions' (see Methods, Data reduction). The cell entries represent the percentage of connections where the tracking led to a connection between the two areas under investigation. Areas are listed in the same order as the macaque connectivity in Table 1 which is also of the same size. 2) The same matrix as in Table 5.1 but with parts of the matrix discussed in the text marked.

Table 6 shows the results for all areas under consideration, effectively mapping a large part of the connectivity of the visual system. There are some differences between table 5 and table 6, these can be explained by a difference in the tracking algorithm used. In all previous results, tracked fibers can only be used once, whereas due to the nature of the scripting algorithm used for this table, a fiber from a certain region can be used to connect to multiple areas. These results will not be described in more depth because our hypotheses are mainly about connections from the subcortical areas.

	LGN	PUL	SC	V1	V2	V3	V3a	V4v	VP	FEF	hMT+	V4	PPA	FFA	LOC
LGN															
PUL	100														
SC	75	65													
V1	85	30	0												
V2	80	25	5	100											
V3	80	25	15	95	100										
V3a	100	50	13	94	94	100									
V4v	80	15	0	95	100	95	100								
VP	60	20	0	100	100	70	56	100							
FEF	30	25	15	0	5	0	0	0	5						
hMT+	15	5	0	0	15	20	25	10	0	25					
V4	33	8	0	33	67	42	63	100	83	0	8				
PPA	55	35	5	70	85	45	75	100	95	0	20	67			
FFA	60	20	15	40	40	35	63	80	50	35	70	83	75		
LOC	45	20	5	20	50	90	100	80	40	35	95	67	70	95	

Table 6: The final connection matrix of all the areas under consideration, using largely the same methods as in Table 5. The difference with the methods used for Table 5 is that in all previous results tracked fibers can only be used once, whereas due to the nature of the scripting algorithm used for this table, a fiber from a certain region can be used to connect to multiple areas. This explains the differences between table 5 and table 6. Again, cell entries represent the percentage of connections where tracking led to a connection, in this table rounded to whole percentages.

Discussion

For each of four main results (see table 5) we shall discuss *a)* the results in the group connectivity matrix, *b)* compare this to the known connectivity in the monkey brain (see table 1), *c)* the results in individual subjects and if applicable *d)* the actual fibers from the tracking (see figure 2-4 after the conclusion). Note that if in the text below we state that “no connection has been found in the monkey data”, we mean that the integrated resulting connection in the Cocomac-database returns ‘no connection found’, which is not necessarily the same (For more details see Kotter, 2004; Stephan *et al.*, 2001) .

LGN – Early visual

In the group results of table 5 it is clear that a large amount of connections have been tracked from the LGN to the early visual areas (part I in table 5.2). The connections to V1, V2, V3 and V3a have been tracked in 75 – 100 percent of the possible cases where this connection could be tracked. This is not surprising as the connections between the LGN and the early visual areas is probably one of the

most well known connections in the visual system. Still, the fact that this connection has been found might serve as a ‘benchmark’ for our method, as it shows we are capable of finding the connections we are sure exists.

However, some aspects of these connections are not exactly what we expected. First of all, the most well known connection, between the LGN and V1 is found in 80 % of the connections whereas the connection between the LGN and V3A, which is much more uncertain, was found in 100% of the tracked connections. Furthermore, if we compare this part of the matrix to the macaque connectivity matrix in table 1 we see that the connections between the subcortical areas and V3, V4v and VP apparent in our results, were not found in the monkey tract tracing data. These unexpected results can be explained in two ways. First of all the delineation of primary visual areas through retinotopic mapping is not necessarily very exact or objective even when using supposedly more objective methods like field sign mapping (Serenio *et al.*, 1994) as was noted in the previous chapter. This is especially true when delineating bordering areas. Therefore there is a certain chance a connection that is found to run to V3A or V3 is actually to V2. A second reason for the unexpected part of this result, especially the fact that the connections from LGN to V1 is not found in 100 % of the possible connections, is the variance over subjects. In three out of five subjects (1, 3 and 5) 100 % of the possible connections have been successfully tracked between these areas, one subject has 75 % of these connections, but one subject has very low percentage of these connections which brings down the average (subject 2, 25 %). The very high percentage for the connection to V3A might be partly explained by the fact that some V3A’s were not found (see table 1), increasing the chances for this connection to be found in 100 % of the cases, because there are simply less connections between which this connection can be tracked at all.

To see if the connections between LGN and V1 have been reliably tracked in all subjects we can look at the actual fibers tracked, in figure 2. Figure 2 shows the actual fibers tracked in 3D space, overlaid on the structural MR-images for reference. All subjects, except subject 4, show connections in both hemispheres. Furthermore, in most subjects the exact pathways the connections take clearly shows Meyer’s loop. Meyer’s loop is the wide three-dimensional arc a part of the optic radiation takes to the primary visual fields. Some other fibers take a different loop known to be the rest of the optic radiation. Some fibers take an almost direct route to V1; these might be erroneously tracked connections. The absence of tracked fibers between LGN and V1 in subject 4 could already be seen in table 4. In this table we can see that in subject 4 only 25 % percent of the connections have been found, meaning that only one of the four possible connections has been successfully tracked, namely the tracking in one direction (‘to-from’ or ‘from-to’) in one hemisphere. So despite some unexpected results and a small number of

erroneously tracked fibers, we can say that overall we have been able to successfully track the pathway from LGN to V1, demonstrating the success of our technique in this regard.

Subcortical connectivity pattern

Another question we can answer with the DTI results is: What is the connectivity pattern between all the subcortical areas? In table 1 we can see that they are maximally connected in the monkey data, meaning that each subcortical area is connected to all other subcortical areas. From the monkey we know that the areas LGN, SC and PUL are all interconnected (see table 1). In part II of table 5.2 we can see that this connectivity pattern resembles the pattern we have found in our human subjects. The connection between LGN and PUL has been found in 100 % of the cases and the connection between the LGN and the SC has been found in 75 percent of the cases. The connection between SC and PUL has also been successfully tracked in 65 % of the possible connections. In the raw data, which still includes the amount of fibers tracked per connection (not shown), a comparatively large amount of fibers were tracked per connection. This might be due to the proximity of the subcortical areas to each other. All in all, the subcortical connectivity pattern found in humans strongly resembles the monkey connectivity data. This makes sense since the thalamus is an evolutionary early part of the brain and is therefore probably shared by many species.

Direct pathways to FEF

Part of the reason for doing this study was that direct subcortical – cortical routes might explain a number of unexplained results from other studies. One of the most striking of these unexplained results is the relatively small latency in FEF in single cell recording studies. The FEF receives its first spike on average after 75 ms after stimulus onset, V1 after 66 ms (Schmolesky *et al.*, 1998), while we know the V1 is directly connected to the LGN but the FEF is supposedly a very high level visual area and many ‘processing steps’ away from subcortical areas (e.g. Felleman and Van Essen, 1991). A possible explanation for this apparently paradoxical finding is a direct route to FEF (Chapter 2). In monkeys this connection has been found from the pulvinar to the FEF. In our current work we have been able to examine this connection in the human brain. In table 5.2 part III we can see that a relatively high percentage of connections have been found from the subcortical areas to FEF. Although 25 – 15 % is relatively high for connections to higher visual areas it is low in absolute numbers. In table 4 we can see that direct connections to FEF were relatively prevalent in subjects 2 and 4. In figure 3 we can look at the tracked connections in both hemispheres in these subjects. The pathways ascending to the right and left FEF each seem to diverge into two major fiber tracks, one leading to the centre of the area, the other more to the peripheral parts (towards the centre of the brain). The centre of the FEF in

these particular localizations corresponds with the classical neuropsychological definition of the FEF by Paus (1996). In another study localizing FEF by Petit and Haxby (1999) an extended area (including the peripheral parts mentioned here) is activated by saccade related activity and a smaller part is activated during smooth pursuit tasks. Since the task we used to localize FEF is purely saccade related it is no surprise our localizers correspond mostly with the extended area. The fiber tracks seem to lead to both the smaller part and the peripheral part separately. In some subjects there are only connections to the peripheral part. It makes sense that if the peripheral parts are indeed responsible for rapid saccades, they should be connected to the subcortical areas via a direct pathway, because this would speed up the time needed for the visual information needed for a rapid saccade to reach the FEF. The connections we have found might be a plausible route to supply that information to the FEF. A possible confound however might be that the tracking from the subcortical areas to the FEF has leaked into the corona radiata, a connection that links the motor cortex with the corticospinal tract.

Direct pathways to PPA and FFA

In table 5.2 part IV we can see that the connections between the subcortical areas and the areas FFA and PPA have also been found relatively often (compared to the other parts of the matrix listing the connections to the higher visual areas). In table 4 we can see that subjects 1 and 5 contribute most to this. If we look at the pathways of the actually tracked connections in figure 4, we see that there is a pathway in both subjects going from the subcortical areas to more anterior areas in a broad arc and then to the PPA and FFA. In subject 5 there is also a more direct route to the PPA in a straight line. Because we have no data on the connection to the monkey equivalent of the PPA and FFA (if an equivalent exist at all), we have no data to relate this pathway to. A direct route to the FFA would be evolutionary beneficial for a social animal like man, as essential faces can be recognized instantly. A direct pathway to the PPA might be beneficial for emergency navigation in three dimensional scenes, but this too is speculation.

Areas not directly connected to subcortical areas

There are also areas which are notably unconnected to other areas we are considering in this paper. These are the SC (see table 5.3 part V), V4, hMT+ and LOC. Not finding in a connection with DT-tracktography does not mean there is no connection. A particular fiber bundle might be lost in larger fiber bundles because the main tensor direction will always follow the larger bundle, (the one-bundle, one direction assumption, see Le Bihan, 2003) and there are several other reasons why a pathway may seem terminated while in reality it is not. Still, some absent connections are particularly remarkable. First of all the lack of connections from the SC (table 5.3 part V) corresponds with the monkey data (table 1). This finding disagrees with Petroni, Panzeri *et al.* (2001) who mention that the fast

connection to FEF (see Direct Pathways to FEF) might be explained by a direct connection from the SC, but there seems to be no such connection. Another notable absent connection is a direct connection to V4. This absent connection was predicted in chapter 2 because V4, although supposedly more directly connected to the subcortical areas than the FEF, has a very late latency (103 ms) compared to the FEF. A direct connection to V4 would counter the theory that the fast latency to FEF was caused by a direct connection which V4 does not have. Any conclusions about connections to V4 however, are hampered by the fact that very few V4's were localized in our subjects (see table 1 and Chapter 3).

The disadvantages and advantages of our method

There are some inherent disadvantages to DTI and fiber-tractography. The 'one-bundle one direction assumption' of the diffusion tensor model is unrealistic in places where fiber bundles with different orientations cross, diverge and converge. This means the model can never recognize the difference between kissing and crossing fibers (Le Bihan, 2003). Even worse, when there are kissing or crossing fibers within a voxel, the model can not even represent such fibers. Furthermore, because of these problems with kissing and crossing fibers, there is a risk of a tracking 'leaking' or 'jumping' from one bundle to the other. One might also argue that the field still lacks a generally accepted statistical rigor. Nevertheless DTI and fiber-tractography remain the only way to ascertain structural connectivity in the human brain in healthy patients over longer distances (Behrens *et al.*, 2003; Kim *et al.*, 2006).

There are a number of advantages of using a large amount of functionally defined volumes of interest as target and seed areas for DT-tractography. First of all, exact functionally defined areas can be used for each subject instead of areas based on generalized and/or normalized definitions or non-functional parcellation schemes. Second, multiple areas from multiple parts of the visual system can be studied (e.g. subcortical, early visual and higher visual areas) so that a large-scale structural connectivity model can be studied. Lastly, the exact same areas can be used to study a different type of connectivity (e.g. effective connectivity) and the results can be compared.

This technique of combining fMRI for localization and DT-tractography to study the large-scale connectivity of the visual system has been used before to look at connectivity between striate and extra striate areas (Kim *et al.*, 2006). In this study the thalamic structures were left out, so subcortical-cortical connections could not be studied. We have argued, like Mountcastle (1998) before us, that these areas should not be left out because it makes the model incomplete and because including subcortical-cortical connections increases the predictive power of the model (Chapter 2). Furthermore we have localized a larger part of the visual

system than this earlier study. If, in the future, we were to also include intra-cortical connections in our analysis it would be interesting to compare the two studies.

Earlier research has been done with probabilistic DTI to study the large-scale connectivity pattern between subcortical structures and cortical areas (Behrens *et al.*, 2003). However, this was an exploratory study that looked only at the likelihood of connectivity between the thalamus and very broadly defined ‘cortical zones’. Although informative about the representation within the subcortical areas, this technique is not specific enough to inform us about connectivity between (functionally defined) areas and therefore cannot answer specific cognitive or functionally defined questions, nor does it enable any comparison with other primate structural connectivity data.

Comparing human and monkey connectivity data

If we compare the monkey brain connectivity matrix from the Cocomac-database (Table 1) and our summing matrix representing the connectivity in the human brain (Table 5) we see some striking similarities and differences. The similarities are the strong connections from the LGN to the early visual areas, the connectivity pattern between the subcortical areas and the lack of connectivity from the SC to other visual areas. The differences are the lack of connections from the pulvinar to the visual areas in the human data and the abundance of connections to V3a, V4v and VP in the human data. These differences might be due to the differences between the human and the monkey brain but might also be due to the limitations of DTI mentioned earlier.

Conclusion

The structural connections between subcortical areas and the early visual areas and higher visual areas was studied using DTI and fiber tractography, using functionally localized areas as seed and target areas. As far as we know, we are the first to test a large-scale model of the connectivity in the human visual system including the subcortical areas. Despite the limitations of both the DT-tractography and the functional localizers, a large degree of similarity was found between subjects and between the resulting human connectivity matrix and the monkey connectivity matrix, which shows the connections were reliably tracked. Like in the monkey brain, the connectivity between the LGN and the early visual system was high and the connectivity between the subcortical areas was maximal. Most remarkable new results were the direct routes to PPA, FFA and FEF, these connections might have some evolutionary advantage and might explain some other neuro-scientific results.

Figure 3: Tracked connections from the subcortical areas to the FEF, in both hemispheres, in subjects 2 and 4, both 'to-from' and 'from-to'. The LGN is orange, the pulvinar is brown, the SC is pink and the FEF is green. A coronal slice of the anatomical data has been added for reference. The view is from anterior to posterior.

Figure 4: Tracked connections from the LGN to PPA and FFA, in the right hemisphere, in subjects 1 and 5, both 'to-from' and 'from-to'. The LGN is orange, the PPA is yellow, the FFA is red. A sagittal slice of the anatomical data has been added for reference. The brains are not in ACPC space but in original space hence the different 'angles' of the brain

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Chapter 5

General Discussion

This thesis investigated the connectivity in the large-scale structure of the primate visual system with three methods: computational modeling, fMRI and DTI. In this chapter the results are evaluated in the light of the research goals, to see to what degree these goals have been reached and what questions remain, as challenges for future work.

Summary of the results

In *Chapter 2* latency data and structural connectivity data, both from *monkeys*, were successfully combined. The large-scale topologies that emerged from the data after optimization did not violate any of the known structural connectivity data, yet fit the timing data better than the dominant model of the organization of the visual system (the hierarchical model, Felleman and Van Essen, 1991). The most prominent feature of the best fitting topologies was the large number of connections from the subcortical areas to the cortical areas, both in a small consistent data set and a large summarized dataset. Topologies with such connections were shown to be more constrained by the data than the hierarchical model.

Chapter 3 mapped the large-scale structure of the *human* visual system in single subjects in original space with fMRI. A large number of subcortical, early visual and higher visual areas were localized. The subcortical areas were activated consistently during a saccade task but less consistently during presentation of the customary retinopic stimuli. If there is no need to study the retinotopic structure of the subcortical areas, a saccade task is a more efficient localizer for the subcortical nuclei. We also noted that the extent of the area FEF differs from the classical neuropsychological definition by Paus (1996), probably because we used a saccade task instead of a smooth pursuit task (Petit and Haxby, 1999). The subjective nature of delineating the early visual areas is also discussed.

In *Chapter 4* the structural connectivity between functionally localized areas in the human visual system has been mapped with DTI and fiber-tracktography. The large-scale structure of the human visual system obtained in chapter 3 was used to obtain location and extent of the areas. The structural connectivity of the human visual system is relatively unknown and DTI is one of the few available methods to study human structural connectivity. The main goal was to investigate subcortical to cortical connections and therefore only these connections were tracked. The tracking results are very similar to the known structural connectivity in the monkey visual system, validating the techniques used. Other main results were the relatively high probability of a connection between the subcortical structures and the areas FEF, PPA and FFA. We also find that the superior colliculus is relatively sparsely connected, comparable to what has been found in

the monkey visual system. Current limitations in fiber-tracking methodologies and DTI resolution are also discussed.

Goals

The modeling and experiments in the present thesis addressed three main aims:

1. To map the large-scale structure of the *primate* visual system. This involves mapping both the location and extent of the elements of the visual system and the connections between these elements.
2. Propose new models that suffer less from the problems associated with the older models of the visual system, namely:
  - a. The topologies are often indeterminate (Hilgetag *et al.*, 1996)
  - b. The connectivity matrices are often incomplete (Mountcastle, 1998)
  - c. The areas included in the structure are restricted (Mountcastle, 1998)
  - d. The topologies are incompatible with latency data (Bullier and Kennedy, 1983; Nowak and Bullier, 1998; Schmolesky *et al.*, 1998)
  - e. The structure of the models can not explain the residual functioning of the visual system in blindsight (Goebel *et al.*, 2001) and Riddoch syndrome patients (Hinrichs *et al.*, 2006; Schoenfeld *et al.*, 2002)
  - f. The topologies are often method dependent (Chapter 2)
3. To achieve these aims by using convergent evidence (Baars, 2007; Gazzaniga *et al.*, 1998) from multiple species and with different methods.

Evaluating goals

The first goal of mapping the structure of the *primate* visual system has been achieved by creating a map of the *connectivity* of the *monkey* visual system based on structural and latency data, and mapping the *functional organization* and *connectivity* in the *human* visual system with fMRI and DT-tracktography. Our mapping of the human visual system is by no means complete and the reliability of DT-tracktography leaves room for improvement. The question also remains if the results obtained generalize to the *primate* visual system. These questions shall be addressed in more detail in the next sections.

Our second goal of aiming to improve on current models could be divided into several sub-goals and these will be evaluated separately below:

- a. In chapter 2, a model was formulated (Figure 11 of the same chapter) that was less *indeterminate* than its most prominent predecessor, the hierarchical model (Felleman and Van Essen, 1991). Hilgetag *et al.* (1996) pointed out that the hierarchical model could be reformulated in a large number of ways with elements being moved in the model without violating any constraints. Although we used a different cost-function and a different way to visualize the number of possible different models, figure 9 in chapter 2 shows that our method of visualizing ‘constrainedness’ produces similar results for the

hierarchical model as the method used by Hilgetag *et al.* (1996). More importantly, this figure also shows that adding more types of data, as we have done in chapter 2, constrains the model more.

- b. A problem with earlier models of the visual system was the fact that their connectivity matrices contained empty entries, so that they were *incomplete*. The results in this thesis provide information about the connectivity of the visual system in both monkey and human, filling in gaps in monkey and human connectivity matrices, making the connectivity matrices ‘less incomplete’ or ‘more complete’. In chapter 2 we show that the introduction of subcortical – cortical connections explains latency data in a model of the monkey visual system. These connections have been traced before in monkeys but were never included in a large-scale model of the visual system. By adding these connections we have made the monkey connectivity matrix more complete. In chapter 4 we have tracked the connections from the subcortical areas to the cortical areas of the human visual system with DT-tracktography. Most of these connections have never been studied before, so adding these connections to the matrix yields a more complete matrix of the human visual system. It should be noted that both results are indirect evidence of these connections.
- c. Previous models of the visual system did not include connections to and from the subcortical areas and connections to and from the contra-lateral hemisphere and where thus *restricted* (Mountcastle, 1998). By adding the subcortical areas and their connections to both monkey and human models of the visual system (chapters 2, 3, and 4), we have improved these models. However, connectivity between hemispheres remains largely uncharted territory.
- d. In chapter 2 we have shown that the model proposed by us in that chapter has improved the agreement with the timing data as compared to that of the hierarchical model (see figure 8 and 5 of the same chapter). We also show (as illustrated in figure 10 of the same chapter) that all inconsistencies between timing and topology have been resolved.
- e. As we have first argued in chapter 2, the fact that patients with unilateral lesions in the early visual system have activity in the higher visual areas that was comparable with activity in the undamaged hemisphere (Goebel *et al.*, 2001; Hinrichs *et al.*, 2006; Schoenfeld *et al.*, 2002), could be explained by direct routes from the subcortical areas to the cortical areas in the visual system. In chapter 2 we have shown that these routes have been found with the use of tract tracing studies and that it is plausible that these routes are used during the ‘feedforward sweep’ in visual processing. The results from the human connectivity study are less clear on this matter. On the one hand, subcortical routes have indeed been found in humans, but on the other hand

the areas that were measured having normal activity (hMT+, LOC, V4) have not been found to be connected.

- f. In chapter 2 we have argued that in the past, the structure of models of the visual system was very much dependent on the kind of data used to constrain the model and the phenomena it was designed to explain, whereas these models should have agreed as they describe the same physical system. Mapping the monkey visual system by integrating two methods mitigates this problem of ‘method dependence’ but does not solve this problem completely, because we do not know what would happen to the structure of our model when more (kinds) of data are added. This problem is addressed in the next section.

Our third goal, to use converging evidence (Baars, 2007; Gazzaniga *et al.*, 1998) from multiple species and with different methods to verify our hypotheses, has also been achieved. First, our hypothesis emerged from a modeling study that combined latency data and structural connectivity data. The first attempt to verify this hypothesis used the Cocomac-database (Kotter, 2004) to find monkey studies that successfully traced this connection. The second attempt to verify this hypothesis used fMRI and DT-tracktography to test if there were direct subcortical connections in the human visual system. All in all, we have used multiple techniques from computational neuroscience (modeling, database collation of data, tracktography) classical neuroscience (tract tracing studies) and cognitive neuroscience (fMRI, DTI) in both monkeys and humans to verify our hypotheses.

Open questions

In this thesis we have attempted to map the structure of the primate visual system, using converging evidence from multiple methods and species. However, the differences and similarities raise a new question: Is the structure of the visual system fixed or dynamic?

Fixed or dynamic

Taken together, Figures 1 and 11 in chapter 2 show five distinct models of the monkey visual system (Andersen *et al.*, 1990; Felleman and Van Essen, 1991; Petroni *et al.*, 2001; Zeki and Shipp, 1988), including the model proposed in that chapter. All these models have markedly different topologies although they refer to the same system. The differences must be caused by differences in the data, the methods employed, or the different organizational principles. This ‘approach-dependency’ was also mentioned in chapter 2 as a limitation of earlier models. It seems that the structure of a model changes with the kind of data of organizational principle used to constrain the model. There may be two causes for this: (1) All these models reflect the same underlying *fixed* structure that could be revealed by

integrating all the results upon which they are based, or (2) different kinds of processing require different routes through the system, meaning that the functional structure of the system changes *dynamically* to accommodate ‘task demands’, this would mean the anatomical structure is fixed but the functional structure is dynamic. One could argue that the structure of the visual system is fixed when comparing the results for dataset 1 and dataset 2 from chapter 2 as both results, from different datasets, show roughly the same structure. On the other hand, a recent fMRI paper suggests the processing hierarchy for faces and objects might be different (Lerner *et al.*, 2001) and this could be seen as supporting the view that there are indeed different, dynamically organized systems adjusted to task demand. In this case the model proposed in chapter 2 might be a structure that is perfectly adjusted to first spike processing during the feed-forward sweep, but that a different task requires a totally different system. Expanding our model might help to resolve this issue. If a new type of constraint is added, preferably a correlate of a different kind of processing, and further ‘solidification’ of the model can be observed, then this could be interpreted as support for the single-hierarchy or single organizational principle view. If, on the other hand, we then find that a totally different kind of structure explains the new combination of data best, the dynamic-organization view is more likely to be correct. However, even if we assume that the dynamical-organization view is correct, we know the anatomical structure of the brain is not flexible enough to change fast enough to accommodate task demand. Therefore the anatomical structure of the visual system might be fixed (or limited in its flexibility by the amount of neural plasticity) while the functional organization of the visual system is adjusted according to the task demand to the brain. This would mean that the functional organization is constrained by the structural connectivity but not vice versa.

Describing brain topologies

In this thesis we have attempted to describe different models of the visual system or more specifically their organizational structure or topology. This has sometimes proved to be difficult due to the lack of proper terms to describe brain topologies. For instance if we try to compare the hierarchical model proposed by Felleman and Van Essen (1991) and the model we proposed in chapter 2 (see figure 11 in chapter 2) we could say that the model we propose is ‘flatter’ but this is not a very clear description. We could say it is more ‘parallel’ where as the hierarchical model is more ‘serial’ as these terms are related to the flow of information or electricity through a network. This seems more accurate and descriptive and indeed some authors have attempted to use these terms to describe a network structure (see e.g. Bullier *et al.*, 1995), but these terms become unpractical in more complex situations. For instance, how would we describe the structure used by Petroni *et al.* (2001) shown in this same figure (figure 11, chapter 2)? Or how could one describe the entire structure of the network proposed by Felleman and

Van Essen (1991) seen in figure 1, in these terms? A possible solution is to quantify the terms parallel and serial (e.g. so that $1 - \text{'parallelness'} = \text{'serialness'}$). An existing method that describes organization of networks quantifiably is the 'small world' methodology (Watts *et al.*, 1998), it has been successfully applied to brain networks (Salvador *et al.*, 2005; Klaas E. Stephan *et al.*, 2000) and uses two terms to describe networks namely characteristic path length and clustering coefficient. More 'quantifiable descriptive terms' like this might be developed to describe brain networks by using methods from graph theory. For instance, we could describe the human intra-subcortical structure from chapter 4 (see table 5) as a 'complete bipartite graph' instead of 'completely connected graph'.

Human visual system

We have argued that the work in this thesis improves the 'completeness' of the monkey connectivity matrix and enhances the constraints placed on a model of the connectivity of monkey visual system. We have met these goals for the human visual system to a lesser degree. Studying connectivity in the human brain is restricted due to the limitations in current anatomical labeling techniques; tracing can only be done for distances of tens of millimeters and then only in the major pathways (Behrens *et al.*, 2003; Kim *et al.*, 2006). Therefore, large parts of the human connectivity matrix remain empty, making the model incomplete. At the moment one of the few alternatives is using DTI and fiber-tractography, but that technique also has its limitations. The resolution of DTI is far coarser than the size of neural fibers, and because diffusion tensor models can only represent one main direction per voxel this means this direction is only a 'summary' of the neural fibers in the voxel. This means that if a connection cannot be tracked between two areas this is not conclusive proof that this connection does not exist, because a fiber tracking will be wrongly terminated when the fiber-bundle crosses a larger fiber-bundle. If a connection can be tracked between two areas this is not conclusive proof that it exists as a tracking may have 'leaked' or 'jumped' from one bundle to another. Even if we know what the main bundles are, and we can observe that a tracking has 'leaked' we cannot be certain that there is no actual connection between these fiber-bundles at that point. We have tried to overcome this limitation in chapter 4 by reporting the chance of a certain connection being tracked between two areas, but at the moment, DT-tracktography can only constrain a connectivity model to a limited degree. Summed up, we might say that although we have made the human connectivity matrix more complete and more determinate, there is still a lot of room for improvement.

Primate visual system

Another aim of this thesis was studying the *primate* visual system. But do our data really provide enough constraints to form a model of the primate visual system? If we collate the resulting matrix from chapter 2 (e.g. figure 4 from chapter 2), the

monkey connectivity matrix from the Cocomac-database (table 1 from chapter 4) and the matrix obtained with DT-tracktography in humans (table 5 from chapter 4), what will match and what will be hard to collate? All results presented in this thesis, from both monkeys and humans, seem to show that direct connections via de superior colliculus are implausible, and that there is some level of connectivity between the subcortical areas and the cortical areas. Another strong similarity between human and monkey data is the maximum interconnectivity between the subcortical areas. However, whereas the human results show more direct connections via the LGN, the monkey results have more direct connections via the pulvinar (as a case in point, table 1 shows connections from the pulvinar to all cortical areas under consideration in this thesis). Another clear dissimilarity was that there was a high possibility of tracking a connection with DT-tracktography between the LGN and V3a, V4v and VP, while the monkey connectivity matrix does not have these connections. This might be due to a number of reasons; the subjective nature of delineating early visual areas, the limitations of DT-tracktography or it might be due to a genuine difference between the visual system of humans and monkeys. In the end, one might argue that if the differences between models of the monkey visual system (described in the paragraph *Fixed or Dynamic*) are still large, settling on a single topology for the primate visual system (like Tootell *et al.*, 2003 have done for the functional organization of the visual system) might be premature.

To \ From	PUL (pulvinar)
V2	Benevento <i>et al.</i> , 1975, 1976
V3	Rockland <i>et al.</i> , 1999
V4	Adams <i>et al.</i> , 2000
MST	Boussaoud <i>et al.</i> , 1992
FEF	Romanski <i>et al.</i> , 1997
MT	Sincich <i>et al.</i> , 2004

Table 1: Authors that have found connections from the pulvinar to cortical areas, for all connections from the Pulvinar to cortical areas in consideration in this thesis.

Future directions

Modeling propagation speed and variance in the visual system

The results from chapter 2 can probably be improved most by adding an extra constraint in the form of propagation speed. Although we are convinced that a difference in propagation speed between the parvo- and magno- cellular pathways cannot explain all latency differences, we are also convinced that a speed difference does exist and is even already apparent in the latency data used in dataset 1 of chapter 2 (Schmolesky *et al.*, 1998). The challenge however is modeling this propagation speed, as very little is known about actual propagation speed in the visual system, and it is difficult to estimate propagation speed in a pathway because each pathway consists of three types of neurons. (For more

details see chapter 2.) However, systematically varying the propagation speed may yield some interesting results. It might be possible that there are sets of propagation speeds that can reproduce the observed onset latencies with little, if any, violations of the known connectivity of the system. Then it would be particularly interesting to see if such sets can reproduce the systematic conduction differences in the dorsal and ventral stream.

We might further improve the biological plausibility of a future modeling study by using a type of stochastically firing neuron in the model to try and account for the apparent increasing variability in first spike latencies in areas further removed from the input node. The second latency dataset used in chapter 2 (from a meta-analysis by Lamme and Roelfsema, 2000) does not include variances, but the variances in the data of the original studies could be used.

Functional and Effective connectivity

In this thesis we have explored structural connectivity in both monkeys and humans. There are however two lines of investigation that remain unexplored: 1) using *effective connectivity* measures with *single cell recording* data in monkeys and 2) using functional and effective connectivity to study the *large-scale* connectivity of the human visual system. 1) An example of how we could look at the effective connectivity in spiking data from monkeys would be to adapt an effective connectivity measure like Granger causality from the fMRI domain (Goebel *et al.*, 2003; A. Roebroeck *et al.*, 2005) or Partial Directed Coherence from the EEG domain (Kaminski *et al.*, 1991) to the spiking data domain and apply it to a dataset like that of Schmolesky *et al* (1998). This would be a good dataset for this goal but any dataset that results from a measurement of a large amount of simultaneous micro-electrode recordings in the visual system will do. 2) Testing the effective connectivity in the large-scale organization of the human visual system is relatively straightforward if this organization is known in individual subjects. The study done in chapter 3 provides a method to obtain this organization. If the exact location and extent of the areas in the system is known in all subjects, all that is needed is an extra scan session in which functional data can be acquired on which Granger causality (Goebel *et al.*, 2003; A. Roebroeck *et al.*, 2005) or Dynamic Causal Modeling (Friston *et al.*, 2003; L. Lee *et al.*, 2006; Penny *et al.*, 2004) can be applied.

Probabilistic framework for connectivity

In this thesis a number of studies have been done into the large-scale connectivity of the visual system in two species, using a large amount of methods. While this has been presented as an advantage, the downside of this approach has also been discussed: it is harder to generalize all finding into a general model. However, there might be a way to combine all the information from all these studies. Human

and monkey brain data, for example, have been combined before in a probabilistic atlases (Van Essen *et al.*, 2007). If we were able to integrate all data into a Bayesian model (see T. S. Lee *et al.*, 2003 for an example of the visual cortex) in which each connection in the connection matrix is estimated by a probability that sums up all possible data thus far on this connection, data from different approaches and species could be integrated into a single model. Such an approach allows for a more generic model but averages out differences between subjects and species. Alternatively models could be confined to single subjects or species, yielding more specific models. The advantage of the Bayesian approach is that new evidence is readily incorporated in the model through Bayesian updating.

Processing models of the visual system

In this thesis computational modeling, classic neuroscientific data and brain imaging were used to reveal the connectivity of the visual system. These methods were used in succession, but if we want to understand what actually happens within and between active brain regions, a combination might be even more productive. Insights might be gained by developing large-scale *processing* models, in which biologically inspired artificial neural networks are used to explain (among others) fMRI, DTI and single-cell recording data (Goebel, 2007). Integrating neuroscientific data with large-scale neural network models will force us to develop more detailed information processing models, as the representations and computations within areas will have to be specified. These models should not only account for neuroscientific data in its original biological representation (e.g. spike-trains in cells, BOLD signals on cortex meshes) but should also model the overall ‘behavior’ of the whole system at some level. For instance, a modular neural network might be devised that has a module for each area in the visual system. This model could then be made to accommodate measured BOLD responses obtained with fMRI, connectivity obtained with DTI and be able to recognize objects. This model has the potential to tell us something about possible representations within a module or about the nature of a signal between modules or it might be used to distinguish between two possible topologies of the system. These kinds of models could maintain the differences between subjects or species without limiting the generalizability, and integrate both timing and localization data. All in all, processing models might stimulate the integration of large sets of isolated empirical findings into coherent candidate theories of complex brain function, not only in the visual system.

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Samenvatting

Stel, u wordt op een dag blind wakker. U zou zich al snel realiseren hoe belangrijk visuele perceptie is en tegelijkertijd hoe vanzelfsprekend het is als u gewoon kan zien. Het deel van de hersenen dat verantwoordelijk is voor visuele perceptie, *het visuele systeem*, kan onderverdeeld worden in hersengebieden, waarbij elk gebied een specifieke functie en locatie heeft. Om te begrijpen hoe het visuele systeem werkt, is het van belang te weten hoe die verschillende gebieden met elkaar verbonden zijn, oftewel wat de *connectiviteit* van het visuele systeem is. Dat is niet alleen van belang om te kunnen achterhalen hoe de verschillende gebieden met elkaar samenwerken maar het kan ook van belang zijn bij patiënten met hersenbeschadiging. In dit proefschrift wordt de connectiviteit van het visuele systeem onderzocht met verschillende methoden. Allereerst zijn er computermodellen gemaakt van het visuele systeem van apen, vervolgens zijn bij mensen de locatie en omvang van de belangrijkste hersengebieden van het visuele systeem in kaart gebracht, en ten slotte zijn de verbindingen tussen deze gebieden onderzocht met moderne biomedische beeldvormingstechnieken.

In **hoofdstuk 1** wordt een inleiding gegeven in de hersenstructuren en methoden genoemd in dit proefschrift. De paradoxen en problemen in de hedendaagse kennis over het visuele systeem worden eveneens beschreven. De hersenstructuren die betrokken zijn bij visuele perceptie zijn onder te verdelen in drie groepen: de sub-corticale kernen, de ‘vroege’ visuele gebieden en de ‘hoge’ visuele gebieden. In de ogen wordt licht dat op de retina valt omgezet in een neurale signaal. Dit neurale signaal gaat eerst naar de *sub-corticale kernen*. In dit proefschrift zijn vooral de Lateral Geniculate Nucleus (LGN), de Superior Colliculus (SC) en de Pulvinar (Pul) van belang. Deze kernen dienen waarschijnlijk als ‘schakelstations’ voor het neurale signaal. De ‘vroege’ visuele gebieden worden zo genoemd omdat men ervan uitgaat dat het neurale signaal na de sub-corticale kernen eerst naar deze gebieden toe gaat. De vroege visuele gebieden beschreven in dit proefschrift zijn: V1, V2, V3, V3A, VP en V4v. Deze gebieden onderscheiden zich van andere gebieden doordat zij een topografische representatie van de buitenwereld bevatten. De ‘hoge’ visuele gebieden (V4, MT, MST, FEF, LOC, FFA and PPA in dit proefschrift) danken hun naam aan het feit dat zij verantwoordelijk zijn voor de ‘hogere’ functies van het visuele systeem, namelijk het herkennen van bepaalde kenmerken van de visuele wereld zoals bijvoorbeeld kleur (V4), beweging (MT) of gezichten (FFA). Men gaat ervan uit dat het visuele signaal van de sub-corticale kernen naar de vroege visuele gebieden gaat en daarna pas naar de hogere visuele gebieden. Deze aanname wordt echter in twijfel getrokken in dit proefschrift.

Er bestaan verschillende onderzoeksmethoden om het visuele systeem te onderzoeken. In dit proefschrift zijn de volgende methoden van belang: tracers, microelectrode recording, fMRI en DTI. Met *neuro-anatomische tract tracing* methoden oftewel *tracers* kan een onderzoeker vaststellen of twee hersengebieden door neuronen verbonden zijn. Dit gebeurt door een bepaalde stof in te spuiten in het ene gebied en vervolgens te kijken of deze stof aankomt in het andere gebied. Bij *microelectrode recording* steekt men een elektrode rechtstreeks in een hersengebied om vast te stellen wanneer het neurale signaal aankomt in dat hersengebied. Dit noemt men ook wel *single unit recording* of single cell recording. Voor beide methoden moet men het hersenweefsel beschadigen en daarom kunnen deze methoden alleen bij proefdieren gebruikt worden. Voor het onderzoek in dit proefschrift zijn deze methoden niet gebruikt, wel is uitgebreid gebruik gemaakt van eerder met deze methoden verzamelde gegevens. Voor de studies in dit proefschrift is gebruik gemaakt van fMRI en DTI. Met *functional Magnetic Resonance Imaging* (fMRI) kan gemeten worden welk deel van het brein actief is tijdens het uitvoeren van een bepaalde taak. Met *Diffusion Tensor Imaging* (DTI) kunnen de verbindingen tussen de verschillende hersengebieden in kaart gebracht worden. Beide technieken zijn onschadelijk voor een proefpersoon en kunnen daarom op mensen toegepast worden. Daar staat wel tegenover dat deze technieken alleen indirect bewijs leveren, in tegenstelling tot de eerder genoemde methoden.

De huidige modellen van de structuur van het visuele systeem bevatten een aantal problemen en paradoxen. Ondanks uitgebreid onderzoek in dit veld zijn de huidige modellen zeer verschillend van structuur. De beschikbare onderzoeksresultaten leiden niet tot een eenduidige structuur en de structuur van het model blijkt vaak afhankelijk te zijn van de gebruikte onderzoeksmethode. Tevens zijn de modellen niet compleet en zijn zij beperkt tot een bepaald deel van het visuele systeem. Daarnaast zijn er recente onderzoeksresultaten die niet verklaard kunnen worden door de huidige modellen. Zo laat fMRI-onderzoek zien dat patiënten met beschadigingen in de vroege visuele gebieden toch nog vrijwel normale activiteit hebben in de hoge visuele gebieden, terwijl single unit recording onderzoek laat zien dat het visuele signaal soms tegelijk of eerder aankomt in de hoge visuele gebieden dan in de vroege visuele gebieden. Beide resultaten zijn moeilijk te verklaren met de assumptie dat het visuele signaal altijd van de sub-corticale kernen via de vroege gebieden naar de hoge gebieden gaat.

In **hoofdstuk 2** wordt daarom gezocht naar een nieuw model van het visuele systeem, waarmee de bovenstaande paradoxen wellicht beter verklaard kunnen worden en enkele problemen opgelost. Zoals hierboven beschreven lijkt de structuur van het visuele systeem in sommige gevallen niet compatibel met de timing in het visuele systeem; het visuele signaal komt bijvoorbeeld eerder aan in

de FEF dan in V2, terwijl V2 veel lager in de structuur staat dan de FEF. Daarom hebben wij een nieuwe *computationele* methode ontwikkeld waarbij we de gegevens over timing en structuur combineren, om op zoek te gaan naar een model dat beide soorten gegevens kan verklaren. De connectiviteitsdata komen uit een database waarin vele honderden tracer studies van het apenbrein zijn gecombineerd (www.cocomac.org). De timing data komen uit eerder gedaan single unit recording onderzoek. Uit de resultaten blijkt dat een structuur waarbij de sub-corticale kernen direct verbonden zijn met de hogere visuele gebieden (de vroege visuele gebieden worden dus ‘overgeslagen’) wel compatibel is met de al bekende structuur- en timing data. Tevens tonen we aan dat de nieuwe structuur die wij voorstellen de paradox weldegelijk oplost - in tegenstelling tot eerdere studies – en dat de nieuwe structuur ‘dwingend’ genoeg is om tot een eenduidige structuur te leiden. Deze sub-corticale verbindingen zouden ook de eerder genoemde fMRI-resultaten kunnen verklaren; het bestaan van een directe route naar de hogere visuele gebieden zou verklaren waarom mensen met zwaar beschadigde vroege visuele gebieden normale activiteit kunnen hebben in de hogere visuele gebieden. In hoofdstuk 3 en 4 wordt daarom een poging gedaan om ook de connectiviteit van het menselijk brein in kaart te brengen.

In **hoofdstuk 3** worden de visuele gebieden in kaart gebracht met fMRI, zodat vervolgens de verbindingen tussen die gebieden onderzocht kunnen worden. De belangrijkste hoge visuele gebieden, vroege visuele gebieden en sub-corticale kernen worden hiertoe gelokaliseerd. De sub-corticale kernen worden zelden bestudeerd, maar zij zijn hier van belang omdat wij specifiek op zoek zijn naar verbindingen tussen deze kernen en de hogere visuele gebieden. Om al deze gebieden en kernen te lokaliseren zijn de proefpersonen gescand in een MRI-scanner terwijl zij naar visuele stimuli keken die ontworpen zijn om specifieke gebieden te activeren. Op deze manier zijn met fMRI de LGN, de SC, de PUL, V1, V2, V3, V3A, VP, V4v, hMT+, FEF, FFA, PPA, LOC en V4 gelokaliseerd. Hierbij moet worden opgemerkt dat hoewel de locatie van de gebieden op deze manier betrouwbaar vastgesteld kan worden, de exacte omvang van de gebieden afhankelijk is van de gehanteerde statistische drempelwaarde. Het lokaliseren van V4 bleek minder succesvol dan verwacht. Opmerkelijk was dat de stimuli ontworpen voor het lokaliseren van FEF effectiever bleken voor het lokaliseren van de sub-corticale kernen dan de origineel daarvoor ontworpen stimuli. Door de gelokaliseerde gebieden te projecteren in de originele MRI-beelden van het brein van de individuele proefpersonen, zijn deze lokalisaties zeer geschikt als startpunt voor onderzoek naar connectiviteit in het menselijk brein.

In **hoofdstuk 4** wordt de connectiviteit in het menselijk brein onderzocht. Er is nog relatief weinig bekend over de verbindingen in de hersenen van de mens, omdat de gebruikelijke onderzoekstechnieken niet of slecht toegepast kunnen worden op de mens. In dit hoofdstuk wordt DTI gebruikt om de verbindingen in

het visuele systeem in kaart te brengen. Met DTI kan de ‘hersenvezelrichting’ in het hele brein van levende mensen gemeten worden. In principe wordt de waterdiffusie gemeten, water diffundeert namelijk sterker in de richting van de vezel dan in andere richtingen. Met deze gegevens is het mogelijk om door middel van *vezeltractographie* te onderzoeken of de hersenvezels een aaneengesloten baan vormen tussen twee hersengebieden. Om de locatie en omvang van de gebieden te achterhalen gebruiken we de resultaten uit hoofdstuk 3. Vanwege de resultaten uit hoofdstuk 2 werden de sub-corticale verbindingen in het bijzonder onderzocht. Het feit dat de verbindingen waarvan het bestaan zeker is (tussen de sub-corticale kernen en de verbinding van de LGN naar V1) betrouwbaar gevonden werden, verleent enige validiteit aan de rest van de resultaten. We vonden relatief veel verbindingen tussen de sub-corticale kernen en de hoge visuele gebieden FEF, PPA en FFA. De Superior Colliculus, ook een sub-corticale kern, was echter met relatief weinig gebieden verbonden.

In dit proefschrift wordt bewijs geleverd voor de stelling dat een model van het visuele systeem met daarin verbindingen tussen sub-corticale kernen en hoge visuele gebieden twee paradoxen kan oplossen, terwijl het minder nadelen heeft dan eerdere modellen. In **hoofdstuk 5** wordt uitgebreid ingegaan op deze conclusie. Tevens wordt beschreven hoe de connectiviteit van het gehele visuele systeem het beste beschreven kan worden. Is dit afhankelijk van de taak die het systeem op dat moment uitvoert? Staan de verschillen tussen het apen- en het mensenbrein een generalisatie in de weg? Als laatste worden de mogelijkheden voor verder onderzoek beschreven. Het modeleerwerk uit hoofdstuk 2 laat een duidelijke vraag open. Kan de paradox tussen structuur en timing ook verklaard worden door verschillende signaal-doorgeef-snelheden in verschillende typen neuronen? Met de structuur uit hoofdstuk 3 als beginpunt kan de connectiviteit van het menselijke visuele systeem ook onderzocht worden met functionele en effectieve connectiviteit. Met Bayesiaanse statistiek zouden nog meer soorten data over de connectiviteit van het visuele systeem tot één model gesmeed kunnen worden. Tenslotte wordt de mogelijkheid geopperd om procesmodellen te maken waarbij biologisch plausibele, artificiële neurale netwerken de met fMRI gemeten hersenactiviteit verklaren.

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Veel plezier en blijf leren!

Curriculum vitae

Michael Capalbo was born on Februari 11th 1977 in Eindhoven, The Netherlands. He attended the Lorentz Lyceum in the same city. Before graduating from secondary school in 1995 he won the Dutch national title English public speaking. From 1995 to 1999 he studied psychology at Maastricht University, specializing in cognitive psychology and educational psychology. In 1999, during his research traineeship under the supervision of Dr. Hans Phaf at the University of Amsterdam, he investigated if the dual-route theory of fear conditioning could explain effects of suboptimal priming, in a modeling study. From 2000 to 2002 he was an instructor at Maastricht University, specializing in ICT-supported teaching. From 2002 to 2007 he was a PhD student and junior lecturer at the department of Cognitive Neuroscience at the Faculty of Psychology of the same university. During this period he performed the modeling study described in chapter two of this thesis under supervision of Prof. Dr. E. Postma of the Maastricht ICT Competence Centre (MICC). The fMRI and DTI experiments in this thesis were performed at the Maastricht Brain Imaging Centre (MBIC) under the supervision of Prof. Dr. R. Goebel. In 2006 Michael won the award for best teacher of the year at the Faculty of Psychology. He will continue to work at the department of Cognitive Neuroscience as an assistant professor.