Brain state and changes of mind: Probing the neural bases of multi-stable perceptual dynamics
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Chapter 1

Introduction
Consciousness, then, does not appear to itself chopped up in bits... A “river” or a “stream” are the metaphors by which it is most naturally described. In talking of it hereafter, let us call it the stream of thought, of consciousness, or of subjective life.

- William James (1890)

The internal state of our cerebral cortex changes continuously. Cortical state changes alter the mode in which cortical circuits operate, and they are evident in the temporal structure of neural population activity (Steriade, 2000; Harris and Thiele, 2011; Lee and Dan, 2012; Zagha and McCormick, 2014). The major sources of these state changes are the neuromodulatory systems ascending from the brainstem, such as the diffuse release of acetylcholine from the basal forebrain over the cerebral cortex (Lee and Dan, 2012).

Traditionally, changes in cortical state have been exclusively associated with slow fluctuations in the level of wakefulness (Steriade, 2000; Harris and Thiele, 2011; Haider et al., 2012). But recent work is beginning to reveal that similar changes in cortical state are continuously taking place even during full wakefulness (Harris and Thiele, 2011; Reimer et al., 2014; Zagha and McCormick, 2014) and that neuromodulatory systems may also be transiently activated during specific and rapid cognitive processes such as perceptual inference, attention, and decision-making (Aston-Jones and Cohen, 2005; Gilbert and Sigman, 2007; Parikh et al., 2007; Harris and Thiele, 2011). These transient neuromodulatory events and resulting changes in cortical state may have important, but so far largely unknown, effects on subsequent information processing in the cortex and, hence, subsequent perception, cognition, and behavior.

To illustrate, consider the picture in Figure 1. If you have never seen this image before, you likely see nothing particular, even if you study it for some time. But after convincing yourself there is nothing there, please turn this page to see what is in fact depicted (Figure 2). As it turns out, you were looking at a degraded photograph of a well-known domesticized herbivore. Very likely, knowing the solution has triggered a sudden change in the state of the visual processing machinery in your cerebral cortex at the moment you looked back at Figure 1. This cortical state change resulted in a profound (and, in this case, lasting) change in the way the same image is processed and represented in your brain. In other words, the perceptual switch, evoked by the solution, triggered a change in cortical state that makes your new perceptual state permanent.
What are the cognitive factors that drive such rapid changes in cortical state? Can we measure them in the human brain? And what are their effects on subsequent perception?

To date, the neurophysiological properties of fast changes in cortical state and their consequences for perception are unknown. In this thesis, I will explore the factors that drive these fast state changes in human visual cortex, how these state changes relate to phasic neuromodulatory events, and how they affect perception. To this end, I will use different neuroimaging measures (MEG and fMRI) to uncover complementary features of the neural population activity in visual cortex (in terms of its temporal and spatial structure), which help differentiate cortical state changes from representations of the sensory input. Further, I will use so-called bistable perceptual phenomena as a psychophysical tool throughout all my experiments. What is remarkable about these phenomena is that perception continuously switches back and forth between distinct subjective interpretations of a constant stimulus for as long as people look at the stimulus (Leopold and Logothetis, 1999; Kim and Blake, 2005). I will explore a novel idea about the possible role of global cortical state changes in perception – namely, that changes in global brain state are triggered by the perceptual switches, and, in turn,
have a profound influence on the subsequent perceptual dynamics by stabilizing a newly selected perceptual interpretation for some period of time. A few previous reports have alluded to similar ideas (Leopold et al., 2002; Einhauser et al., 2008) but the general notion of an active mechanism that changes cortical state, and thereby transiently stabilizes perception, differs substantially from current standard accounts of the mechanisms of bistable perception (reviewed below in the section Current models of the visual cortical interactions underlying bistable perception) (Aston-Jones and Cohen, 2005).

Below, I will first motivate the focus on visual perception and specifically bistable perceptual phenomena as an experimental tool to study these state changes. Then I will present a class of computational models of the factors that cause the switches in bistable perception. After pointing out existing evidence for rapid state changes during both bistable perceptual phenomena and other perceptual tasks, I will consider modulatory brainstem systems as a possible underlying mechanism. The chapter concludes with an outline of this thesis.

**Using visual cortex as a model system for understanding cortical processing**

Using tasks in the visual domain makes it possible to build on the knowledge of one of the best-understood functions of the human brain: the processing of visual information. This process starts with the propagation of visual information from the eye, via the optic nerve and the thalamus to a specialized region in the back of the brain known as the visual cortex (Figure 3). The visual cortex consists of a complex hierarchy of many sub-regions that are specialized for different types of visual information (Grill-Spector and Malach, 2004). Neurons in so-called “early” visual regions, such as the primary visual cortex (V1), respond primarily to specific stimulus features, for example specific line orientations in the picture in Figure 1. From V1, this information is fed forward to regions higher up in the hierarchy (V2 and above), which respond to increasingly more complex stimulus features, such as shapes. The visual cortex is retinotopically organized, so that every location in the visual field is represented at a specific location within every sub-region (Wandell et al., 2007).
Bistable perception as a tool to study the functional origins and consequences of cortical state changes

The solution to Figure 1 has changed your perception of this image forever, as you cannot go back to “unseeing” the animal. Thus, this type of stimulus yields only a single perceptual switch, precluding experimental analysis of the corresponding change in brain state. In bistable perceptual phenomena, in contrast, abrupt switches in perception occur continuously despite an unchanging stimulus, as if the brain constantly changes its mind. Thus, these phenomena allow for the generation of countless cortical state changes, making them an excellent tool for studying the state changes. Famous visual bistable phenomena that can readily be experienced are the Necker cube (Figure 4A) (Necker, 1832) and Rubin’s vase-face figure (Figure 4B) (Rubin, 1958). Strikingly, bistable illusions can even render a salient stimulus completely invisible. For example, in binocular rivalry (BR), dissimilar stimuli presented separately to the two eyes compete for perceptual dominance (Figure 4C) (Blake and Logothetis, 2002; Alais and Blake, 2005). Finally, during motion-induced blindness (MIB), a small but clear “target” stimulus completely disappears from perception for some time when surrounded by a moving pattern, only to reappear seconds later (Figure 4D) (Bonneh et al., 2001). Please note that throughout this thesis, I use the term “state change” to refer to a change in the dynamics of cortical activity and not the change in subjective perception of the observer (for instance the perceptual switches from target visible to invisible states in MIB that trigger the cortical state changes).

Besides yielding a large number of state changes in little time, there are more reasons why bistable phenomena are a useful experimental tool for studying the origins and consequences of rapid cortical state changes. Most importantly, bistable phenomena
enable us to study the bidirectional link between cognitive factors (in this case, perceptual dynamics) and cortical state changes: they allow us not only to investigate whether the switches in perception trigger cortical state changes, but also what impact the state changes, in turn, could have on perception, for instance by stabilizing perception for some time. Bistable percepts differ in terms of their stability, defined as the duration of a percept from the moment of switching. These durations are highly variable, even within an observer, and show stochastic independence, so that the duration of the current percept...
cannot be predicted from the duration of the preceding percept (Leopold and Logothetis, 1999). Due to this large variability, percept duration can be used as a trial-by-trial index of the stability of percepts to investigate the role of state changes in shaping the dynamics of conscious perception. The first chapters of this thesis focus on the hypothesis that state changes can stabilize perceptual interpretations.

The later chapters focus on how the perceptual dynamics trigger the state changes. Bistable stimuli are well suited to investigate this relationship, because they allow us to isolate the endogenous (internally generated) changes in brain state from stimulus-related activity, which stays constant over time due to the spontaneous nature of the perceptual switches. In contrast, in other visual tasks, for example detection tasks (Ress et al., 2000; Moradi et al., 2007), observers are required to detect small changes in the visual stimulus. In these tasks, a change in brain state around a perceptual decision is always accompanied by a change in the stimulus, precluding a firm conclusion about its cause. MIB has the additional advantage over other bistable phenomena that the bistable target stimulus is limited to a very specific location in the visual field, instead of the complete stimulus. This feature can be exploited to decouple the neural representation of the small target stimulus (which is confined to a specific location in each sub-region of visual cortex) from retinotopically global modulations of neural activity, such as changes in brain state (Donner et al., 2008, 2013). Hence, I focus on MIB for studying the state changes in this thesis.

Finally, bistable percept dynamics resemble the dynamics of many higher-order cognitive acts, such as thought and exploratory decision formation. Although the process of switching itself seems random, distributions of bistable percept durations are highly predictable and consistent and have a similar shape as distributions of thought and decision formation durations. These distributions are characterized by a sharp rise at shorter durations and a long tail towards longer durations and are often modeled as a gamma distribution (Figure 5). Further, one observer typically produces similarly shaped distributions across different bistable illusions, suggesting a common mechanism underlying higher-level cognition and bistable perceptual dynamics. Similarly shaped distributions are observed in free-viewing fixation times in infants and naïve adults (Harris et al., 1988), fixation durations in cognitive tasks (Suppes et al., 1983), and look durations in young infants viewing a stimulus (Rubin, 1958). Finally, the rate of perceptual switching is correlated with intelligence (Crain, 1961), personality variables (Meredith, 1967), and...
mood disorders (Hunt and Guilford, 1933; Pettigrew and Miller, 1998; Leopold and Logothetis, 1999), suggesting that bistable perceptual dynamics can be used as a marker of cognitive processing. Taken together, these findings suggest that bistable perception can be used as a simple model to identify general principles governing the dynamics of cognition (Leopold and Logothetis, 1999).

Current models of the visual cortical interactions underlying bistable perception

What causes the dynamics of bistable perception? A class of current standard computational models of the neural interactions in visual cortex during bistable perception provides an insight (Figure 6). This model consists of two populations of neurons driven by distinct stimulus components, for example, the two types of gratings in the binocular rivalry stimulus (Figure 3C), or the target and mask in the MIB stimulus (Figure 3D). These populations are subject to several forces that affect their level of activity. First, there is slow decay in activity due to sensory adaptation. This adaptation effect results from the decreased firing of neurons after prolonged stimulation by a stimulus (Alais and Blake, 1999). Second, the populations compete with each other by mutual inhibition, in which increased activity in one population suppresses activity in the other (van Loon et al., 2013). Finally, the populations are subject to random fluctuations of neural activity (“noise”) (Moreno-Bote et al., 2007). The interaction between adaptation, mutual inhibition and noise gives rise to spontaneous transitions between dominance of one of the two populations (Moreno-Bote et al., 2007), which are thought to underlie the perceptual switches (Noest et al., 2007) (Figure 6).

Various studies have isolated modulations of neural activity that presumably play a causal role in prompting the illusory perceptual switches. These modulations have
been interpreted as causal because they precede the transition and are absent when the perceptual switches are evoked by physical stimulus changes (Lumer et al., 1998; Sterzer and Kleinschmidt, 2007; Britz et al., 2008; Donner et al., 2008, 2013) Notably, in the case of MIB, these modulations are confined to sub-regions in visual cortex that represent either the target (visual region V4) or the mask stimulus (intra-parietal sulcus) (Figure 7). Similar competition dynamics have been observed during binocular rivalry (Logothetis et al., 1996).

**Evidence for global state changes in visual cortex during perceptual switches and choices**

An increasing number of studies report fast and global modulations of activity in the cerebral cortex that seem to belong to a completely new and unexpected class of signals. Specifically, during MIB, a fast, widespread modulation of fMRI-activity occurs around the “decision” that the target has disappeared, which is tied to a behavioral report (e.g. a button press) (Donner et al., 2008; Hsieh and Tse, 2009; Donner et al., 2013). Similar modulation occurs during a replay condition, in which the perceptual switches are not illusory, but evoked by physical target offsets and onsets on the screen. This finding indicates that the modulation is not related to the cause of the spontaneous disappearance, because then it would only have occurred during MIB, but not replay. These modulations are neither represented in classical models of bistable perception and also not in the older measurements of single-unit activity during bistable tasks (Logothetis and Schall, 1989, 1990).

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**Figure 6 | Architecture of a standard class of bistability models**

Two neural populations ($X_1$ and $X_2$) are driven by distinct inputs ($I_1$, $I_2$). The populations compete via mutual inhibition, and both populations are subject to slow adaptation dynamics and random fluctuations of neural activity (“noise”). The interplay of excitation, inhibition, adaptation and noise underlies the dominance of the populations and consequently dominance in perception.
The characteristics of the modulation of fMRI-activity in MIB suggest that the modulation reflects a rapid change in brain state during perceptual switches (Donner et al., 2008). Following the target-specific suppression of fMRI-activity (Figure 7), a modulation occurs throughout early visual cortex, the sign of which reflects the type of switch that subjects reported: negative for disappearance, positive for re-appearance. Thus, the modulation is not indifferent to the type of switch, as would be expected from attention. Second, the modulation occurs even in regions of visual cortex that are not stimulated by the target and mask stimuli, indicating that the modulation is not due to a change in the strength of the stimulus representation in visual cortex. Third, during replay, the modulation seems more closely time-locked to the report of the switch than to the corresponding stimulus change, pointing to a top-down origin of the signal. Finally, the modulation depends on task-relevance of the switches, because it does not occur during passive viewing of perceptual switches. Taken together, these findings are consistent with a post-decisional state change in visual cortex. In line with these fMRI-modulations (which are an indirect measure of neural activity), results from local field potential studies in monkey visual cortex and thalamus (Gail et al., 2004; Wilke et al., 2006; Wilke et al., 2009) show similar modulations in the lower frequency bands, suggesting a possible electrophysiological underpinning of these modulations.
These global modulations might be a general phenomenon. Signals suggesting rapid changes in brain state have also been observed during other bistable illusions (de-Wit et al., 2012) and in many other types of perceptual tasks. Several studies reported modulations of population activity in human and monkey early visual cortex, which were largely decoupled from representations of the stimulus in the cerebral cortex, but coupled to behaviorally relevant events (Jack et al., 2006; Wilke et al., 2006; Donner et al., 2008; Hsieh and Tse, 2009; Sirotin and Das, 2009; Cardoso et al., 2012; de-Wit et al., 2012; Swallow et al., 2012; Donner et al., 2013; Choe et al., 2014). Taken together, these signals call for a systematic characterization. In this thesis, I will detail the neurophysiological signals around bistable switches and assess whether they are linked to the stability of bistable perception.

The role of neuromodulatory brainstem mechanisms

What are the sources of the rapid changes in cortical state during cognitive acts? Neuromodulatory brainstem systems are in an ideal position to play such a role, because they exhibit transient activity during perceptual decisions, such as detecting faint stimulus changes or bistable switches (Aston-Jones and Cohen, 2005; Parikh et al., 2007; Einhauser et al., 2008; Hupe et al., 2009; de Gee et al., 2014). Specifically, two neuromodulatory systems are key candidates for state changes in visual cortex during perceptual decisions: the locus coeruleus-noradrenaline (LC-NA) system and the basal forebrain-acetylcholine (BF-Ach) system. Both systems project broadly to the entire cortex, including visual cortex. Both systems also exhibit transient bursts of activity during perceptual decisions. For example, during a visual cue detection task, the medial prefrontal cortex of rats showed transient increases in cholinergic activity in response to detected, but not missed cues (Parikh et al., 2007). Likewise, during an oddball discrimination task, LC neurons in monkeys were phasically and selectively activated by target, but not non-target cues (Aston-Jones et al., 1994). Both these findings indicate that neuromodulatory systems are capable of responding selectively, depending on the content of perceptual decisions. In humans, similar responses have been observed around perceptual decisions in pupil dilation, a putative marker of neuromodulator release under constant lighting conditions (Einhauser et al., 2008; Hupe et al., 2009; de Gee et al., 2014). In the second part of this thesis, I use pupillometry to investigate the relationship between neuromodulatory brainstem systems controlling pupil diameter and rapid changes in brain state.


Outline of this thesis

The first part of the thesis focuses on the hypothesis that cortical state changes shape the time course of bistable perception by stabilizing percepts. Using MEG, Chapter 2 provides a detailed characterization of the neurophysiological signatures of rapid state changes, as well as a test of this hypothesis. The chapter reports a transient, retinotopically widespread modulation of beta (12–30 Hz) frequency power over visual cortex that is closely linked to subjects’ behavioral report of target disappearance in MIB and its replay. This beta-modulation is a top-down signal, decoupled from both the physical stimulus properties and the motor response, but contingent on the behavioral relevance of the perceptual change. Critically, the modulation amplitude predicts the duration of the subsequent target disappearance. The results suggest that the transformation of the perceptual change into a report triggers a top-down mechanism that stabilizes the newly selected perceptual interpretation.

Using a different MEG system and a new group of subjects, Chapter 3 shows that the beta power modulation over visual cortex not only occurs when subjects promptly report the perceptual switches by button press, but also when they covertly count the switches. This finding convincingly decouples the global modulation from the beta modulation over parietal cortex that is related to the motor response used to report switches. This finding adds important further support to the notion that the top-down modulation is related to the decision-making process, but it is not necessarily tied to an immediate motor response to indicate the decision.

A hallmark of bistable perceptual dynamics is the lack of very short-lasting percepts, which is reflected in the skewed percept duration distributions (Figure 5). Chapter 4 employs psychophysics to show that this lack of brief percepts is not due to an inability of observers to report fast switches via button press. Thus, observers experience a genuine lack of short percepts, indicating that perception indeed briefly stabilizes after a perceptual switch.

The second part of this thesis focuses on the role of phasic neuromodulatory events in rapid state changes. The global modulation of fMRI- and MEG-activity during MIB reflects the contents of perception, with opposite signs for disappearance and reappearance. If neuromodulatory systems play an active role in the state changes, then their activity should also reflect the contents of perception. Chapter 5 employs pupillometry,
a peripheral measure of neuromodulator release, to investigate this hypothesis. This chapter shows that switch-related pupil dilation on individual switches indeed encodes perceptual content, with larger amplitude for target disappearance than re-appearance. Independent of this effect, pupil dilation during stimulus-evoked perceptual switches also scales with the level of surprise about the timing of switches.

Using whole-brain fMRI, Chapter 6 specifies the exact spatial extent of the global modulation and examines the relationship between the amplitude of the modulation and pupil dilation at the time of the perceptual switches. The chapter reports the previously observed percept-encoding modulation of fMRI activity around perceptual switches. Strikingly, this decision-related suppression of activity in a non-stimulated part of V1 around target disappearance is stronger when the concomitant pupil dilation is larger. A similar pattern of activity occurs in anterior cingulate cortex, a region with strong projections to neuromodulatory systems located in the brainstem.

Taken together, these results support an active role of phasic neuromodulation in fast changes in cortical state during elementary perceptual decisions. In Chapter 7, I summarize the empirical findings and consider possible sources of the modulation, focusing on neuromodulation. To accommodate these findings, I then incorporate a post-decisional modulatory population into the standard bistability model introduced above. Finally, I discuss the implications of the findings presented in this thesis for other, more abstract types of decision making and psychopathological conditions, such as schizophrenia.