The neural correlates of conscious visual perception in the frontal cortex of non-human primates

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„You've taken your first step into a larger world."

- Master Obi-Wan "Ben" Kenobi to his young Apprentice

Dedication

To my parents

To my uncle, and my grandmother, both of whom passed away while I was here.

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1 ABBREVIATIONS

BR - Binocular Rivalry

PA – Physical Alternation

PFC – Prefrontal Cortex

LFP – Local Field Potentials

SUA – Single Unit Activity

MUA – Multi Unit Activity

MEA – Multielectrode Array

FEF – Frontal eye fields

vlPFC – ventrolateral prefrontal cortex

LPFC – Lateral prefrontal cortex

2 ACKNOWLEDGEMENTS

"We live in a society"; so goes the meme that's all the rage these days. We live in a society, and therefore we have a social contract. A massive part of this social contract is the interdependence between individuals. Gratitude that evolves from this social contract is a cornerstone of modern society. It starts right from the beginning,and so too would I like to begin with my sincerest and everlasting gratitude to my parents – Geetha Dwarakanath and B S Dwarakanath, who brought me into this world and nurtured me throughout. They've been two massive pillars of support upon which stands my entire life. Many thanks also go to all my family who have supported me in my scientific journey throughout –Papakka Ajji (grandmother, RIP), Gurudodappa (who used to bring me charts of the solar system when I was 5) and Pachi (who taught me how to use computers when I was 11 in 1998), Uma (aunt and a 2nd mother to me), another Uma, Gayathri aunty, Srinivas uncle (RIP), Chandra aunty, Dattathri uncle, Suchi, Divya, Shailesha, Vaishnavi, Nagaraju Mama and family, and all the others. Towards the end, a special mention to one of the most important people in my life, my maternal grandmother, Amba Ajji, with whom I lived during my Bachelor's time and who has always been a massive rock. No one cooks like her!

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Research builds on the foundations already laid by the best architects who came before us. We stand on the shoulders of these giants and seek to lift the fog of war from the paths that lie ahead in our journey. Their very lives, illustrious as they are, serve as a font of inspiration to all students of science. Thank you very much for your work, enthusiasm and encouragement to generations of scientists.

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3 SUMMARY

In binocular rivalry, our perception alternates spontaneously between mutually exclusive or mixed interpretations, although the physical stimulus remains constant. This enables us to study visual consciousness, as it allows a dissociation of sensory processing and conscious perception. Previous BOLD fMRI studies in humans have implicated the role of the fronto-parietal network in mediating perceptual alternations. However, the extent and the nature of these modulations has been argued to reflect consequences of conscious perception, like introspection, monitoring and, decision making. To resolve this issue, we used a no-report binocular rivalry paradigm of vertically moving gratings, based on an Optokinetic Nystagmus (OKN) read-out of the content of consciousness.

We show here for the first time that slow cortical states in the delta-theta (1-9Hz), and beta (20-40Hz) regimes in the prefrontal cortex coupled antagonistically are predictive of an upcoming change only when the percept switches spontaneously, but not physically. Physical transitions in the animal's percept manifest themselves strongly post-switch in the same oscillatory range. Moreover, we also show a clear dissociation between the change in the polarity of the OKN and this slow-state activity preceding a spontaneous transition. Furthermore, we find robust modulation in the spiking activity of visually-selective simultaneously recorded neuronal ensembles contingent on the animal's perception. The magnitude of these modulations was comparable to the activity elicited in response to presentation of monocular visual input. Taken together, these results strongly suggest that oscillatory activity in the prefrontal cortex plays a central role in refreshing the content of visual consciousness and spiking activity is modulated in accordance with conscious perception.

4 ZUSAMMENFASSUNG

In binokularer Rivalität, unsere Wahrnehmung wechselt spontan zwischen zwei sich gegenseitig ausschließenden oder gemischten Interpretationen, auch wenn die Stimuli sich nicht ändern. Dieses Phänomen ermöglicht uns, bewusste visuelle Wahrnehmung zu erforschen, weil es uns erlaubt, die sensorische Informationsverarbeitung von der bewussten Wahrnehmung zu trennen. Frühere BOLD-fMRT-Studien ließen die Bedeutung des frontalen und parietalen Netzwerks für die Vermittlung von Wahrnehmungs-änderungen erkennen. Es wurde jedoch vermutet, dass das Ausmaß und die Natur dieser Modulationen Konsequenzen bewusster Wahrnehmung darstellen, wie zum Beispiel Selbstbeobachtung, Überwachung und das Treffen von Entscheidungen. Um diese Frage zu klären, verwendeten wir ein rückmeldungsfreies binokulares Rivalitätsparadigma von sich vertikal bewegenden Gittern, basierend auf dem Auslesen des Bewusstseinsinhalts eines optokinetischen Nystagmus (OKN).

Wir zeigen zum ersten Mal, dass langsame kortikale Zustände im Delta-Theta- (1-9Hz) und Beta- (20-40Hz) Regime im präfrontalen Kortex, die antagonistisch gekoppelt sind, nur dann eine bevorstehende Veränderung vorhersagen, wenn die Wahrnehmung spontan, aber nicht physisch wechselt. Physische Übergänge in der Wahrnehmung des Tieres zeigen sich verstärkt nach dem Übergang im gleichen Oszillationsbereich. Darüber hinaus zeigen wir auch eine klare Trennung zwischen der Änderung der Polarität des OKN und dieser langsamen Aktivität vor einem spontanen Übergang. Des Weiteren finden wir eine robuste Modulation in der Spike-Aktivität von visuell-selektiven, gleichzeitig aufgenommenen neuronalen Ensembles, die von der Wahrnehmung des Tieres abhängig ist. Die Größe dieser Modulationen war vergleichbar mit der Aktivität, die als Reaktion auf die Präsentation von monokularem visuellen Stimulus hervorgerufen wurde. Zusammengenommen deuten diese Ergebnisse stark darauf hin, dass die oszillatorische Aktivität im präfrontalen Kortex eine zentrale Rolle in der Auffrischung des Inhalts des visuellen Bewusstseins spielt und die Spike- Aktivität in Übereinstimmung mit der bewussten Wahrnehmung moduliert wird.

5 LIST OF PUBLICATIONS

NB – An asterisk (*) indicates co-first-authorship.

5.1 ACCEPTED/PUBLISHED

5.1.1 The role of the occipital cortex in resolving perceptual ambiguity

Grassi, P.; Schauer, G.; **Dwarakanath, A**.: The Role of the Occipital Cortex in Resolving Perceptual Ambiguity. *Journal of Neuroscience* 36 (41), S. 10508 - 10509 (2016)

5.1.2 Nonmonotonic spatial structure of interneuronal correlations in prefrontal microcircuits

Safavi, S*.; **Dwarakanath, A***.; Kapoor, V.; Werner, J.; Hatsopoulos, N.; Logothetis, N.; Panagiotaropoulos, T.: Nonmonotonic spatial structure of interneuronal correlations in prefrontal microcircuits. *Proceedings of the National Academy of Sciences of the United States of America* 115 (15), pp. E3539 - E3548 (2018)

5.1.3 Testing the perceptual equivalence hypothesis in mental rotation of 3D stimuli with visual and tactile input

Caissie, A.; **Dwarakanath, A**.; Toussaint, L.: Testing the perceptual equivalence hypothesis in mental rotation of 3D stimuli with visual and tactile input. *Experimental Brain Research* 236 (3), pp. 881 - 896 (2018)

5.2 IN SUBMISSION

5.2.1 Prefrontal state fluctuations control access to consciousness

Dwarakanath, A*.; Kapoor, V*.; Fedorov, LA.; Safavi, S.; Werner, J,: Panagiotaropoulos, TI.; Logothetis.: Prefrontal state fluctuations control access to consciousness. (in submission)

5.2.2 Decoding spontaneous changes in the content of consciousness from prefrontal ensembles

Kapoor, V*.; **Dwarakanath, A*.**; Safavi, S.; Werner, J.; Besserve, M.; Panagiotaropoulos, TI.; Logothetis, NK.: Decoding spontaneous changes in the content of consciousness from prefrontal ensembles (in submission)

6 BACKGROUND

6.1 HISTORY OF VISUAL PERCEPTION

The sensory systems of any organism, however rudimentary, sense various external stimuli in the form of light, sound, electric and magnetic fields, pressure, acceleration, and chemicals among various other inputs, and make possible interaction with the environment and other organisms[1]. Indeed, successful development and specialisation of sensory systems has led to the plethora of diverse life-forms that are successful today on earth. Whether it is simple phototaxis in single-celled life-forms[2] or conscious visual perception[3] in higher mammals, the core loop of sensation-perception-action defines life itself. And this is where our story begins.

Visual perception is the ability to detect light in the visible spectrum and using it to interpret our surroundings. Light emanating from after reflecting off of external sources is focused onto the retina which then converts these electromagnetic stimuli into electrical signals and sends them to the brain for further processing[4]. The question then becomes – How does the brain create seamless objects out of electrical impulses and then bring it to conscious awareness? Therein lies the crux of the research into the visual system.

The Ancient Greeks had two major schools of thought on how we perceive the visual world: The "Emission Theory", championed by Plato and Euclid maintained that vision rays emanating from the eyes and impinging on objects were the cause of perceiving said object, while the "Intromission Theory" line of thought preferred by Aristotle and Galen maintained that visual perception was because of the light emanating from other objects entering our eyes. Both schools of thought however relied on the assumption that there was an "internal fire" in the eyes that interacted with the "external fire" from the objects and caused vision [5]. Although some Greek philosophers implicated the brain in non-visual perception [6], it wasn't until more than a thousand years later that that the latter hypothesis was correctly identified as the most probable candidate. This theory of light bouncing off objects being directed to the eyes was first proposed by Alhazen or Ibn Al-Haytham[4], then based in Baghdad, who carried out numerous experiments on visual

perception, extended Ptolemy's work on binocular vision, commented on the anatomical works of Galen, and also produced the oldest surviving diagram of the brain from the perspective of the visual system. He can therefore be considered the father of the scientific method (a good half a century before Bacon); indeed, as he wrote –

> *The duty of the man who investigates the writings of scientists, if learning the truth is his goal, is to make himself an enemy of all that he reads, and ... attack it from every side. He should also suspect himself as he performs his critical examination of it, so that he may avoid falling into either prejudice or leniency.*

It is then, to our good fortune as visual neuroscientists, that the systematic study of the brain originated in the asking of this fundamental question.

The Renaissance and Enlightenment era ushered in many new philosophical investigations and ideas into the field while also reviving some old ideas, namely the ideas that the eye has special properties like the line of sight and foveal and peripheral vision (Leonardo da Vinci, 15th century), that retinal image plays a central role in perceiving what we see, the optics of how the image is produced on the retina (Kepler, 16th century), and that visual perception cannot be treated simply as a spiritual process but a mechanistic one (Descartes, 17th century). Further advancement in different fields of nascent science, such as optics and histology, and improvements in the quality and sophistication of probing apparatuses set the stage for the next wave of research in the modern era. By applying the newly invented Golgi staining technique to the study of the vertebrate retina and brain, Santiago Ramón y Cajal[7] was able to produce remarkably accurate descriptions of the anatomy of the retina and various other structures. His identification of the neuron as the fundamental building block of the brain kicked off the modern field of neuroscience[5].

6.2 WHY STUDY THE VISUAL SYSTEM?

Any phenomenon in biology must be tackled in two ways, viz., a) the proximate or the "How" question and b) the ultimate or the "Why" question[8,9]. The How question pertains to the mechanisms underlying a phenomenon whereas the Why question seeks to answer the

evolutionary significance. At what point in our evolutionary history did the sensation-perception-action loop pertaining to the visual system become critical to survival remains an open question, especially in primates, since vision is our dominant sensory modality. We are indeed strongly visual animals, as evidenced by the fact that over 30% of our cortical surface is devoted to visual processing (over 50% in rhesus monkeys)[10]. These cortical regions that form the dorsal and ventral pathways of information processing are strongly hierarchically organised in that they display increasing complexity in functional specialisation. For e.g. the V1 (primary visual area) responds to luminance, contrast, and edges via simple cells, the MT/V5 responds to motion, the ITC responds to complex images such as faces (Jennifer Aniston neurons[11]), and so on. The end-station of the dorsal pathway is the ventrolateral prefrontal cortex[12], which is therefore the target of our studies. Furthermore, the higher cortical regions exert downward influence via feedback loops that engage top-down processes such as attention and prediction[13,14].

This wealth of knowledge, starting right from the early 20th century comes to us primarily through systematic anatomical and electrophysiological investigations of the above-mentioned structures in cats and non-human primates due to the remarkable similarity of their visual structures to humans. Indeed, Hubel and Wiesel[15–18] demonstrated that one can infer the functional properties of neurons by showing these neurons bars of light, i.e., abstracted features of objects in the natural world. However, what has sorely been missing is the link between the processing of visual information and the conscious experience of these objects, which began with the seminal work of Mountcastle at Johns Hopkins in the 1960s; him and his colleagues being the first to record from awake and behaving monkeys. It is to address this very question that Francis Crick along with Christof Koch championed the investigation of what he termed the Neural Correlates of Consciousness[19]. We have thus inherited this line of questioning from stalwarts such as Crick, Koch, Salzmann, Mountcastle, Newsome, and our own director, Nikos K Logothetis, who forged a new path by directly investigating multistablity (electrophysiology) in specific macaque visual areas[20–28].

Why did he specifically use multistable perception as a paradigm to probe the NCCs? One of the most significant issues in unraveling the NCCs is that sensory processing and perceptual processing are not distinct in normal perception. Multistability allows us to exactly dissociate these

two independent processes and address one in relation to the other. The following section addresses multistability as a tool to probe visual consciousness in further detail.

6.3 MULTISTABLE PERCEPTION

Generally, object recognition in visual perception is unambiguous and distinct. In rare cases, the same stimulus can evoke multiple interpretations which stochastically transition between these various states. For e.g., the famous Necker cube[29,30] and the duck-rabbit[31] illusions shown below are physically one distinct object; however, our perception of the said object flips between two distinct interpretations. I prefer to delinate multistability into two different types, viz., static multistability where both interpretations are available to the viewer at the same time, allowing volitional "switches" in preferring a given interpretation. This is most clearly observed in the duck-rabbit illusion and the face-vase illusion, among others.

Fixate on the red dot

(a)   (b)
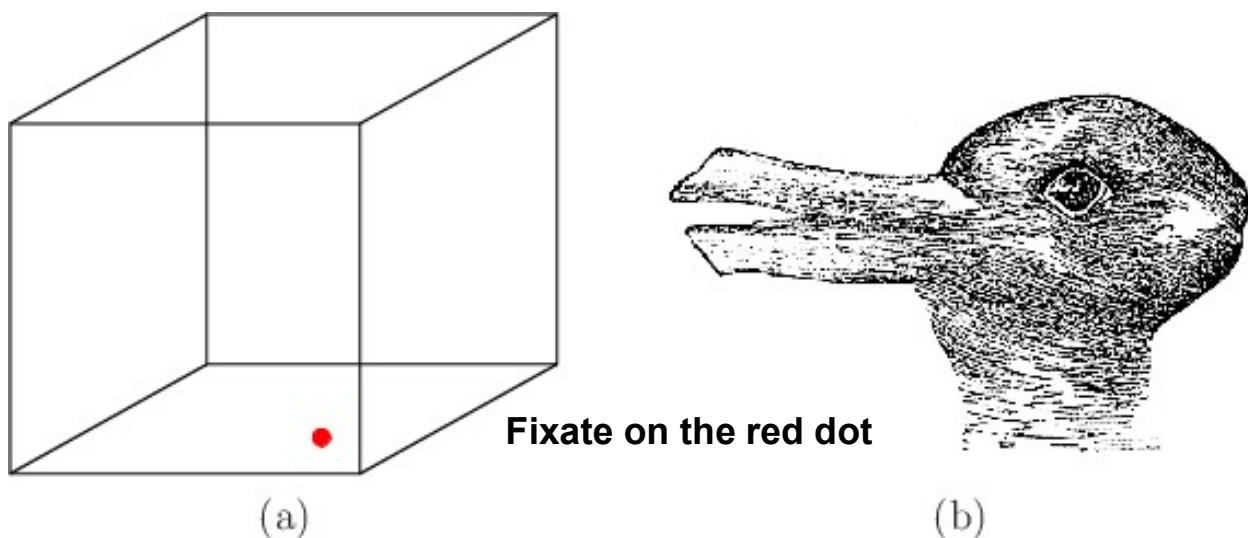
Figure 1 – (a) The Necker Cube. Fixate on the red dot. After some time, the orientation of the cube will start flipping between "up" and "down". (b) The duck-rabbit illusion.

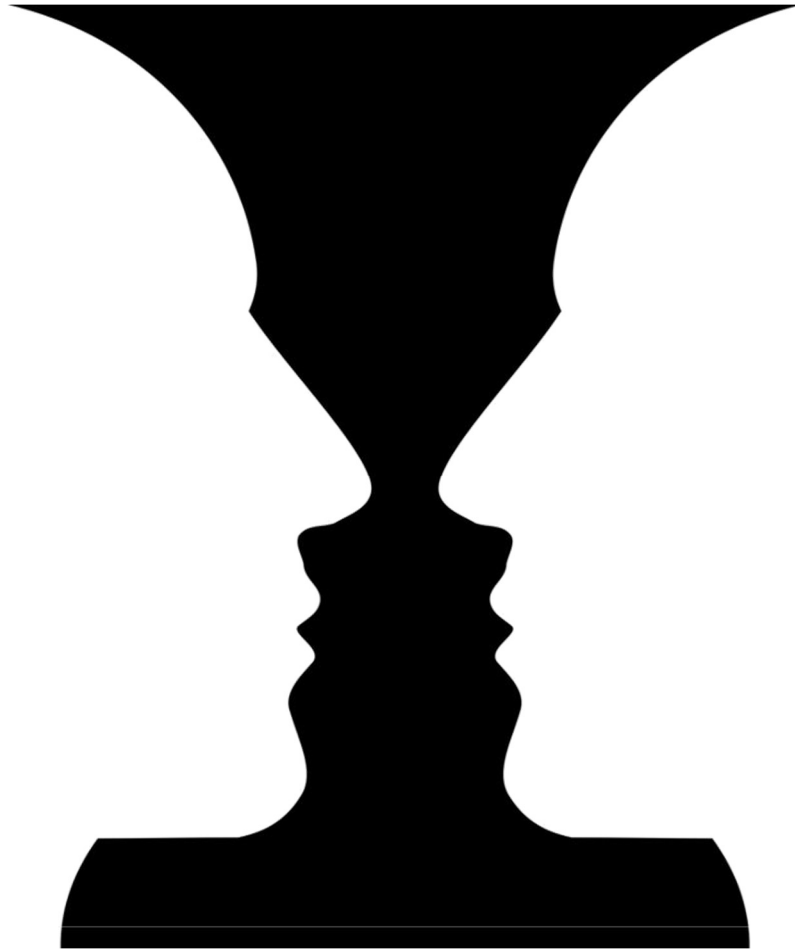*After Steven M LaVelle, UIUC (http://vr.cs.uiuc.edu/node188.html)*

Figure 2 – The face-vase illusion. The black portion of the figure when concentrated upon appears to be a vase. But further inspection reveals 2 faces in white which form the illusory periphery of the vase.

After Rebecca Zarate, UA Magazone (https://www.ua-magazine.com/optical-illusion-what-happens-in-your-head/)

The second type of multistability is what I like to call "Dynamic Multistability". In this phenomenon, a single object can flip between two interpretations (Necker Cube), two different types of structures can arise due to motion (structure from motion[32] – SFM), and global and component motion can compete with each other (moving plaid patterns), among others. Binocular rivalry is a special case of such multistability characterised by the presentation of two distinct and

disparate visual stimuli presented to each eye separately. Inspite of unchanging retinal input, our perception alternates spontaneously between the two presented stimuli and a mixture of the two known as a piecemeal.

The phenonmenon of binocular rivalry has a fascinating history. A young polymath by the name of Giambattista della Porta in the Kingdom of Naples was frustrated by the fact that he could only read and imbibe one book at a time. He reasoned that if he could read two books at the same time, he could accomplish a lot more work. So he did what any one would logically do at that time: he put one book in front of one eye and another book in front of the other eye and attempted to read them simultaneously. To his surprise, he realised that not only could he not read both books simultaneously, but he rather experienced a strange phenomenon wherein, for a few seconds only the first book was "visible", which then changed to the second book, and so on back and forth[33–36]! Dutour[37] and Wheatstone[36] put forth the first modern hypotheses of how this phenomenon might arise. While Dutour favoured the suppression theory, i.e., he believed that because of the "singleness of vision", information from each eye is suppressed at specific times, Wheatstone agreed with Aristotle's fusion view, i.e., images from both eyes are fused to present us our view of the world. He demonstrated the validity of this line of thought by inventing the Stereoscope and discovering binocular stereopsis, which would be impossible with singleness of vision. He wrote about his observations thus in his monograph (Wheatstone, 1838)-

> *"If a and b [which were letters Sand A] are each presented at the same time to a different eye, the common border willremain constant, while the letter within it will change alternately from that which would beperceived by the right eye alone to that which would be perceived by the left eye alone. Atthe moment of change the letter which has just been seen breaks into fragments, whilefragments of the letter which is about to appear mingle with them, and are immediatelyafter replaced by the entire letter. It does not appear to be in the power of the will todetermine the appearance of either of the letters, but the duration of the appearance seemsto depend on causes which are under our control: thus if the two pictures be equallyilluminated, the alternations appear in general of equal duration; but if one picture be moreilluminated than the other, that which is less so will be perceived during a shorter time."*

Binocular rivalry involves sequential, independent, and stochastic transitions between the two presented stimuli. The first systematic study on these temporal dynamics came from a young graduate student called B. B. Breeze, then at the University of Cincinatti, who measured the durations of temporal dominance in a controlled setting[38]. These durations have been shown to be well-approximated by a Gamma function first fitted by Levelt[39], who also discovered the dependence of predominance and suppression on various stimulus dimensions, leading to what are termed the Levelt Laws of Binocular Rivalry[40]. It is interesting to note that while the manipulation of low-level stimulus properties alters the duration of suppression (Levelt's second law), the manipulation of global context in the larger scheme of things, alters the predominance phase while leaving the suppression phases untouched, pointing to two distinct neural processes mediating the same facet of bincoular rivalry[24]. Because of this rich phenomenology, binocular rivalry has become a pre-eminent paradigm in the neurophysiological and neurocognitive investigations into the visual system, both in humans and especially in macaques where invasive recordings are feasible.

Where exactly in the brain does the resolution of this perceptual ambiguity occur? What are its neural correlates? These questions form part of the Holy Grail of understanding visual consciousness. Two primary and contradictory hypotheses have been at logger-heads since the frontal-lobe hypothesis was first propounded by Crick and Koch[41]. Is the front of the brain or the back of the brain, the seat of conscious content?

6.4 THE PHENOMENOLOGY OF BINOCULAR RIVALRY

The neural substrates and the mechanisms that aid in resolving the above described perceptual ambiguity is one of the most important questions in the study of visual consciousness. Historically it was believed that reciprocal monocular inhibition in the primary visual cortex (V1) led to the observed visual competition. However, the discovery of both monocular and binocular V1 neurons that did not follow the percept suggest that monocular inhibition is not the mechanism giving rise to rivalry [22]. Moreover, the percentage of neurons that are modulated by the perceptually dominant stimulus increases along the visual hierarchy [24,28,42–46], pointing to a role of

higher order cortical areas in explicitly representing and potentially refreshing the contents of conscious perception.

Logothetis & Schall (1989); Leopold & Logothetis (1996); Scheinberg & Logothetis (1997); Maier, et al. (2007); Keliris, et al. (2010); Schmid and Maier (2015)
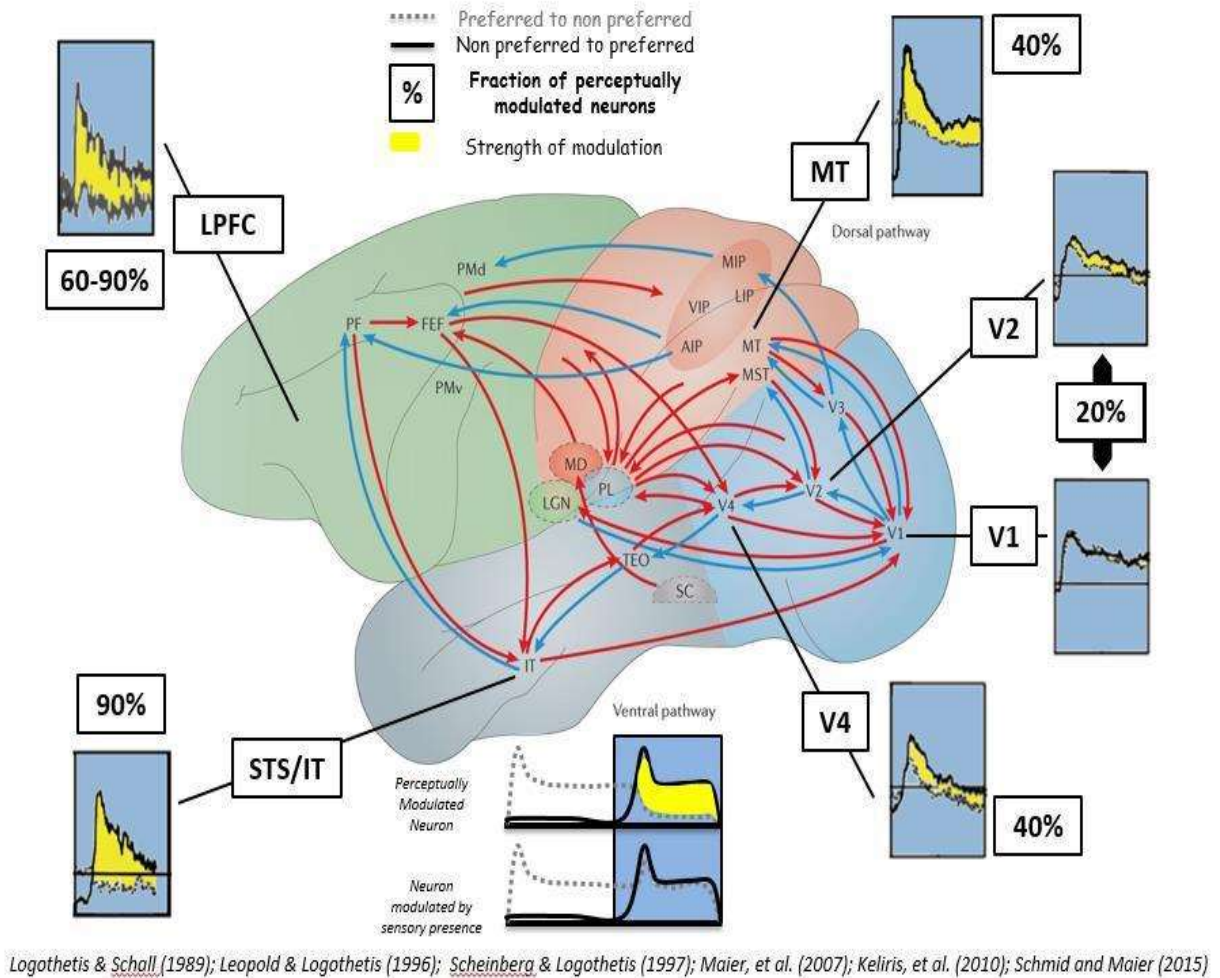
Figure 3 – Percentage of functionally modulated neurons along the ascending visual hierarchy.

Many previous studies in humans with EEG and fMRI have implicated the role of the frontal lobe in mediating perceptual alternations [42,47–52]. Whether this frontal activation is indeed related to the percept, or, is confounded by, or rather reflects the consequences of perception, viz., decision-making, introspection, or motor-output preparation, is still a matter of debate [53,54]. For instance, when humans were instructed to not report their percept, Frässle and co-authors (2014) showed that not only did frontal activity significantly diminish, it led to a global reduction of activity in higher cortical areas, while maintaining activity in the occipital regions, thus igniting the "front vs back" brain debate [55,56]. However, a study by Maier and co-authors using fMRI

recordings and electrophysiology in the macaque V1 has shown a significant divergence of the BOLD signal and the spiking activity of neurons (and the concomitant high-frequency LFP signals) when a percept is actively suppressed (generalised flash suppression), pointing to different temporal regimes of the underlying contributory signals [57]. This study in particular points to the fact that because of this observed divergence, interpretation of cortical activity only using fMRI may be misleading [58,59].

Interestingly, lesion studies in the frontal regions have been inconclusive, having shown both an impairment in being able to switch between the two competing percepts, and no disruption of perceptual alternations [60,61]. Direct electrophysiological recordings from feature-selective single neurons in the lateral prefrontal cortex (LPFC) from macaques [62] and from the medial PFC in humans [63] have demonstrated both a reflection of the content of the conscious percept and activity preceding the perceptual switch. There is still, however, a severe paucity of studies that specifically engage these feature-selective neurons and record from the frontal areas that still maintained activation in the above mentioned functional imaging studies [58], specifically when an objective criterion replaces a voluntary report [64,65]. Most importantly, the specific role of cortical brain states in the form of both ongoing and bursts of activity and their coupling (or decoupling) across different oscillatory regimes and the observed spiking activity as putative neural substrates of visual consciousness has been poorly studied, notwithstanding preliminary results from EEG and LFP studies [66–69].

Another important facet in understanding how changes in conscious percepts are induced, is the nature and role of population activity of a given brain region. Far from being independent decoding units, neurons and neuronal sites act in concert together to make possible a variety of sensory phenomena. A persuasive hypothesis known as the Global Workspace Theory (GWT) [70] posits that for any sensory information to assert itself in consciousness, it must be made accessible to a large variety of connected structures by the collective activation of neuronal sites leading to selection, amplification and broadcasting of this information [71]. A failure in igniting a sufficient number of neuronal sites must then lead to the information being processed subliminally. However, there is scant evidence either supporting or undermining this hypothesis, especially one directly

recorded from higher cortical areas where it has been shown that functional connectivity depends strongly upon feature-selective neurons across long distances [72]. Whether the amplification and broadcast of this perceptual information is mediated via bursts of oscillatory activity, ongoing cortical states, their synchrony, as putative neural substrates, or whether the ignition and broadcast is directly fed forward using the spiking activity of neurons, or perhaps by a multidimensional coupling between the spiking and perisynaptic activity, remains unclear. Moreover, the specific conditions under which a population is ignited, leading to a refreshing of the content of conscious visual perception, is also poorly understood. [62,73–76]

6.5 APPROACH

To address these crucial questions, we employed a no-report paradigm [65] where two oppositely moving gratings and random dot kinetograms at 100% coherence and 100% contrast rivalled against each other, eliciting eye movements called the Optokinetic Nystagmii (OKN). This OKN signal has been previously shown to be an accurate behavioural read-out of perception since it follows the pattern of the moving stimulus [21].
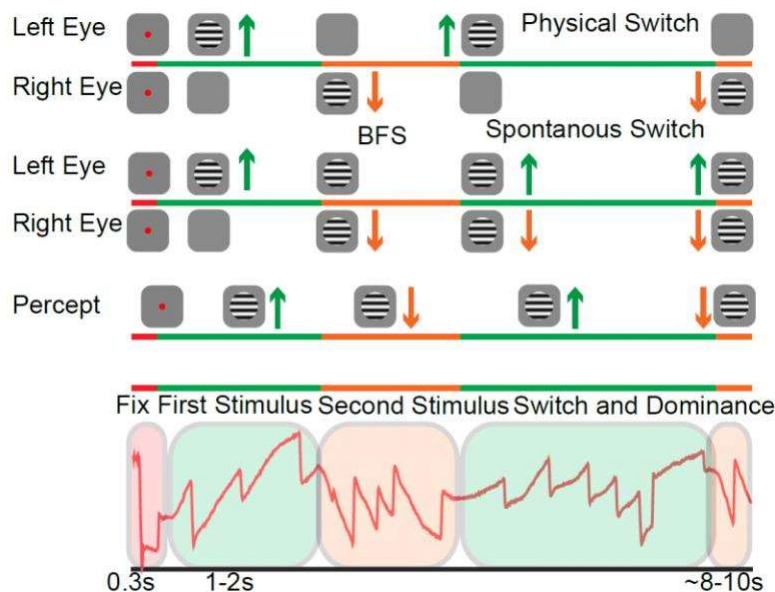

Figure 4 – The experimental paradigm showing both physical alternation and binocular rivalry trials.

We recorded spikes and local field potentials (LFPs) from a 10x10 Utah Array implanted in the ventrolateral prefrontal cortex (vlPFC) of 2 male macaque monkeys while they were engaged in passive viewing of the rivalrous stimuli. Our analysis was predicated upon the identification of spontaneous transitions and piecemeal epochs (mixed interpretation) during the rivalrous periods indicated by a change in the polarity of the OKN complex. Our results show that a temporally linear increase in the amplitude and the number of low frequency (1-9Hz) LFP events during rivalry but not during piecemeals predict an upcoming transition in the content of visual consciousness, whereas such a burst occurs only after an experimentally induced switch, thereby implicating the slow cortical states in causing the content of visual consciousness to refresh.
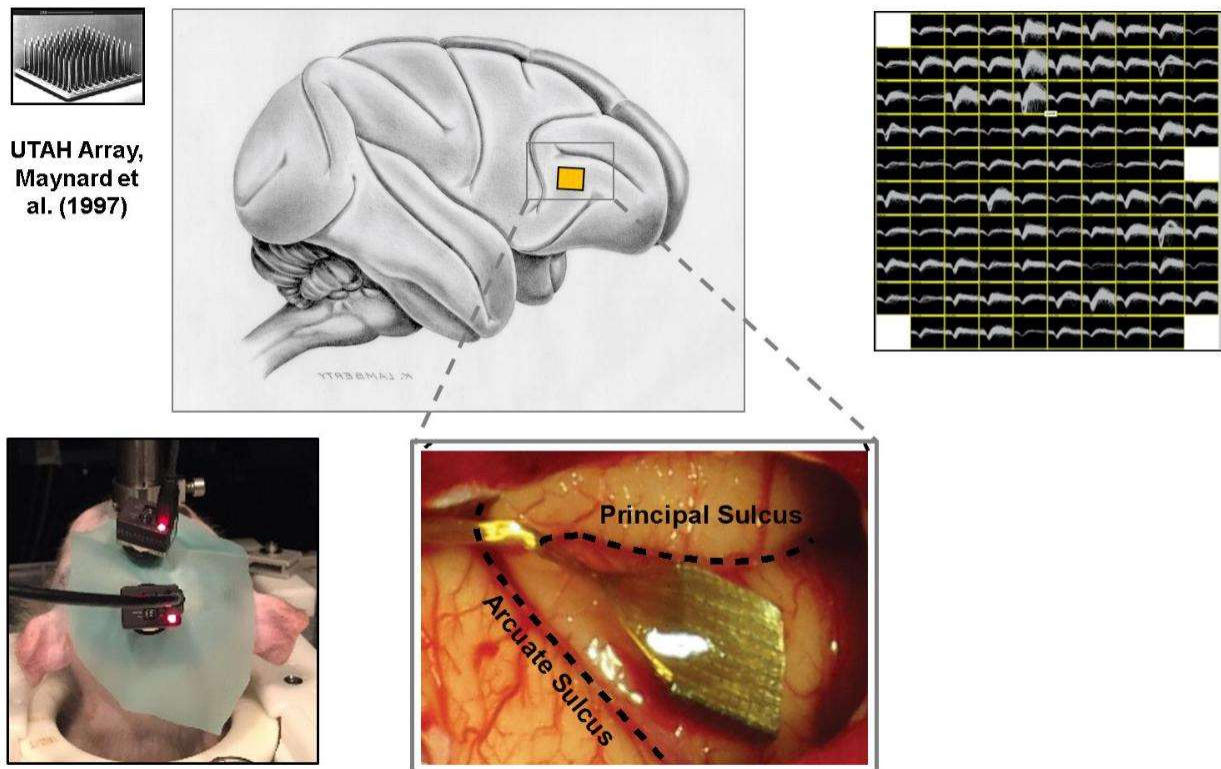

Figure 5 – The Utah array, the implantation region, a live USB plug-and-play monkey (H07), the implant in the brain and the live neural signals.

7 THE ROLE OF THE OCCIPITAL CORTEX IN RESOLVING PERCEPTUAL AMBIGUITY

7.1 MOTIVATION

Many previous studies have employed various experimental paradigms and measurement techniques to try and answer the question of where in the brain is perpetual ambiguity resolved. A recent paper in the Journal of Neuroscience by de Jong and co-authors (2016) - **Intracranial Recordings of Occipital Cortex Responses to Illusory Visual Events –**used electrocorticography in human subjects to probe the electrical activity in the occipital lobe during rivalrous and structure-from-motion stimulation. In both stimulation conditions, i.e., endogenously and exogenously generated switches, they observed a reduction in beta power along with an increase in high gamma power before a transition. We contend that this by itself does not necessarily point to the occipital cortex as the source of resolution of the ambiguity.

7.2 REBUTTAL

We argue that this transient activity in the occipital cortex in and of itself does not point to the stabilisation of a conscious percept. Because they only recorded from the occipital cortex, there is no way of dissociating activity that originates within the cortex vis-à-vis activity that might originate elsewhere and is then conveyed to the occipital regions. Furthermore, if this transient activity indeed resolved the presented ambiguity, it should not manifest itself before a physical transition, which in their data, it indeed does.

Previous studies with fMRI and other global brain measurement techniques have revealed activation during this resolution not only in the occipital, but also in the parietal and frontal regions.

Furthermore, previous studies recording directly from single-neurons in macaque models have shown that single-neurons in the V1 and V4 respond to both the perceived and the suppressed stimuli. Most importantly, previous studies have also shown that along the visual hierarchy, the percentage of perceptually modulated neurons, i.e., the neurons that respond only to the consciously perceived stimulus increase and reach around 90% in the prefrontal cortex.

7.3 CONCLUSION

As Odegaard and colleagues[77] ask, "Should a few null findings falsify prefrontal theories of conscious perception?"; the answer is definitely no. Studies which record from multiple neuronal ensembles from multiple areas simultaneously are the need of the hour to answer this important question. We explore a direct resolution to this problem in the next chapter.

8 PREFRONTAL STATE FLUCTUATIONS CONTROL ACCESS TO CONSCIOUSNESS

8.1 MOTIVATION

Because of the number of previous studies that have reported conflicting results of activation in the frontal areas, with and without report, we implanted a microelectrode array in the ventrolateral prefrontal cortex (vlPFC), which is the terminus of the dorsal visual pathway. Moreover, because of the known domain specificity in the prefrontal cortex, feature selectivity to visual objects has been demonstrated[78]. Most previous electrophysiological studies have only focused on the spiking activity of perceptually modulated neurons[20,23,44,79–84], and have relegated the local field potentials (LFPs) to a subordinate role in information processing. However, recent studies have implicated the roles of different oscillatory regimes in feedforward-feedback loops along the visual hierarchy[85–87]. The particular microelectrode array we use, called the Utah array[88], allows us to simultaneously record LFPs and spikes from a large cortical patch which contains feature-selective neurons, thereby enabling us to investigate the prefrontal neural correlates of consciousness in terms of LFPs and their relationship to spiking activity.

8.2 METHODS

Two adult male macaques (H07 and A11) were trained to follow an upward or downward moving stimulus within a specified viewing window, which resulted in a typical eye-movement pattern called the optokinetic nystagmus (OKN). The polarity of the OKN complex, which is composed of a slow smooth-pursuit following the direction of motion, and a fast corrective saccade to return to the initial viewing point, enables us to decode the active stimulus, and therefore identify points of change in the visual percept[21,89]. The array (4x4mm with a 10 by 10 electrode

configuration and an inter-electrode distance of 400μm) was placed 1 - 2 millimetres anterior to the bank of the arcuate sulcus and below the ventral bank of the principal sulcus, thus covering a large part of the inferior convexity in the ventrolateral PFC, where neurons selective for direction of motion have been previously found. The neural signal was sampled at 30kHz and then band-pass filtered into the LFP and spiking range for further analysis.

8.3 RESULTS

We show for the first time that slow field fluctuations in the prefrontal cortex determine changes in the content of consciousness. Our analysis revealed significant modulation in two distinct bands – the delta-theta (1-9Hz) and the prefrontal beta (20-40Hz) in the recorded LFPs. Whereas the 1-9Hz activity manifested itself strongly as an evoked potential (VEP) after a physical transition, it appeared as diffuse bursts of a collection of events before a spontaneous switch.
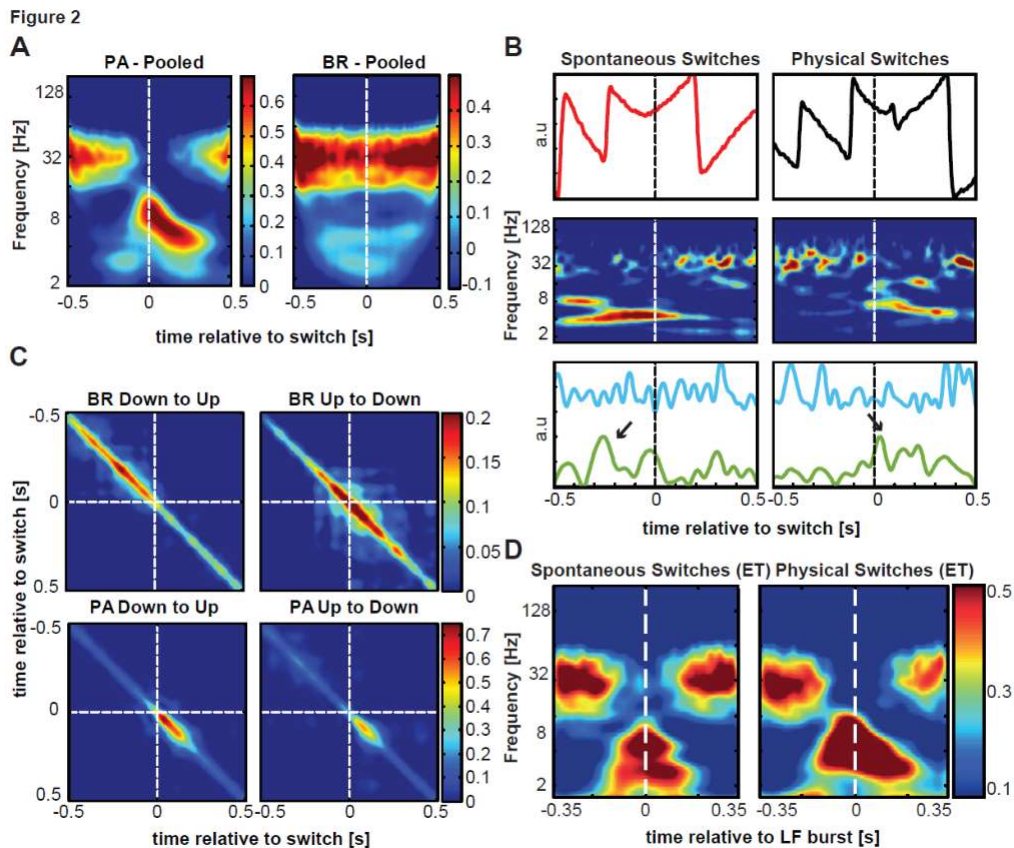

Figure 2

Figure 6 – Time-frequency resolution of the cortical activity around spontaneous and physical transitions (A). Two single examples of switches (BR and PA) – OKN (top row), time-frequency resolution (bottom-row), filtered signals in the two respective bands (bottom row). The same time-frequency resolution of the cortical activity triggered at every low-frequency event (D)

Indeed, both the number and the rate in time of these low-frequency bursts before a spontaneous switch was significantly higher when compared to the same period during physical transitions and then no transitions occurred.
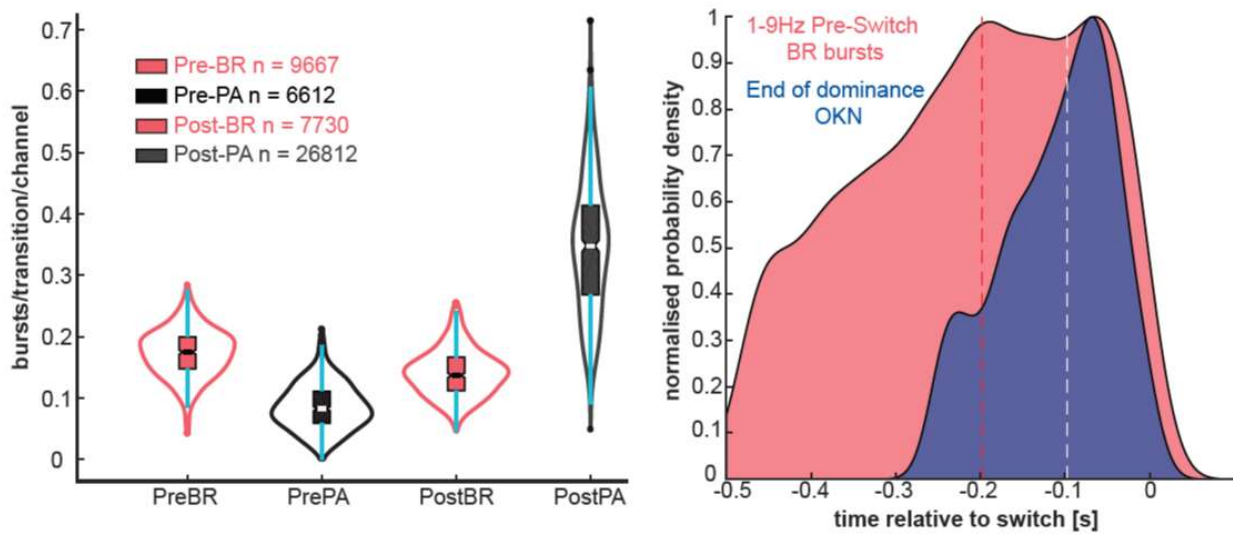
Figure 7 – Burst statistics of the four different windows around switches, both BR and PA (left). Distribution of the burst times of the low-frequency activity compared to the end of the preceding dominance period.

We also observed a non-linear increase in the number of prefrontal sites recruited in time approaching a spontaneous switch, as well as a steady linear increase in the amplitude of these events approaching a switch, pointing to a low-frequency spatio-temporal activation being necessary to induce a perceptual switch.

Figure 8 – Spatiotemporal recruitment of prefrontal sites leading to a spontaneous switch
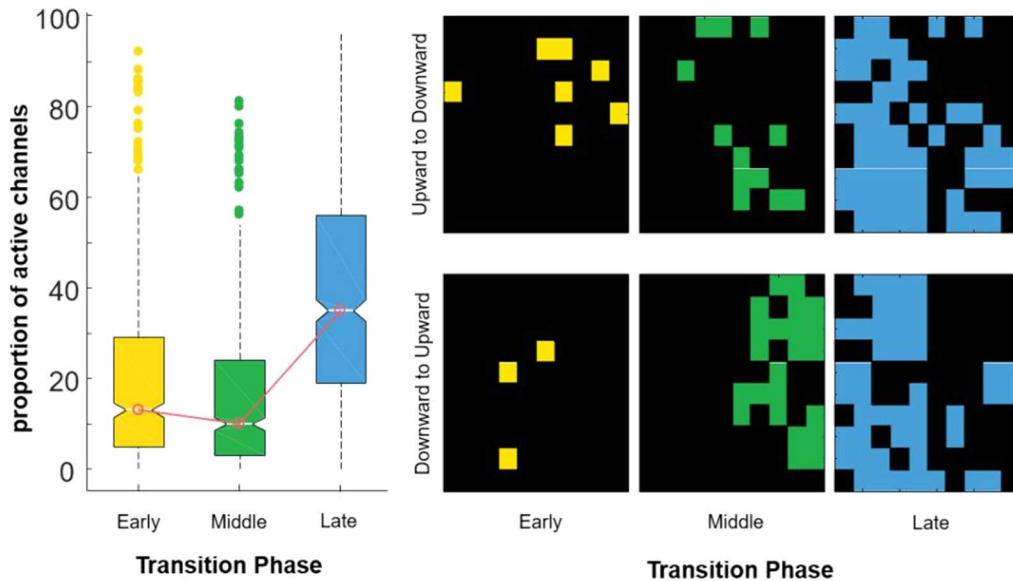
Furthermore, this low-frequency activity was coupled antagonistically to the steady-state prefrontal beta, which displayed a characteristic suppression and rebound after a low-frequency burst. This beta-regime was also locked to the spikes of feature-selective neurons which specifically preferred the dominant stimulus. Finally, the change in the encoding of the active percept in the spiking activity succeeded the low-frequency bursts, pointing to the fact that prefrontal states predict a perceptual switch whereas the feature-selective neurons only report the change in the percept and the current dominance state.
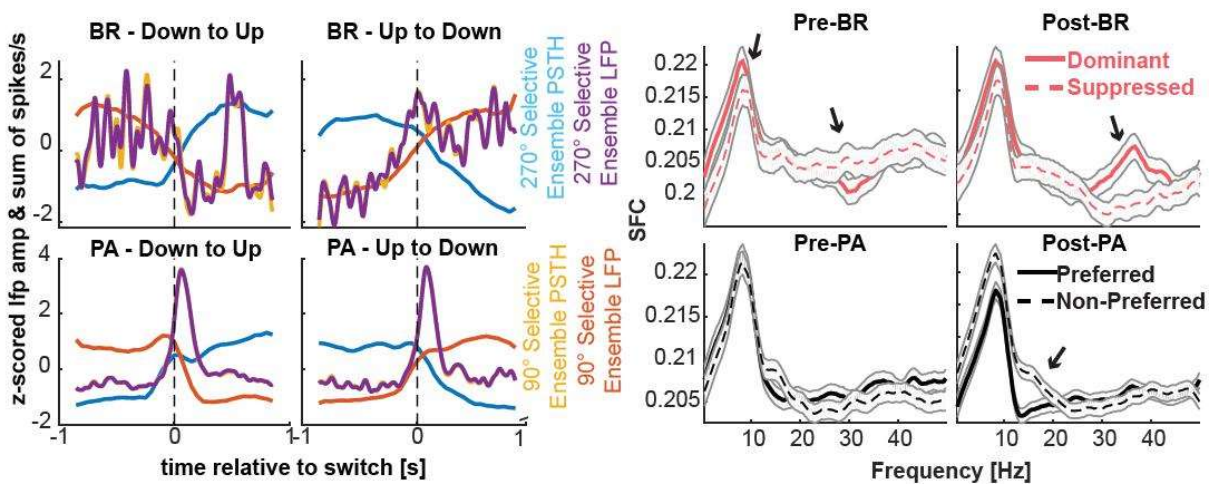
Figure 9 – Spike-LFP relationships around BR and PA switches.

8.4 CONCLUSION

Contrary to the electrocorticography and fMRI results from de Jong et al[54] and Frässle et al[53], we find robust pre-switch activity in the prefrontal cortex in two oscillatory regimes, viz., the 1-9Hz and 20-40Hz during spontaneous transitions but not during physical transitions. We find the prefrontal cortex to be an important and a necessary hub in refreshing and stabilising the content of visual consciousness.

9 DECODING THE CONTENT OF CONSCIOUSNESS FROM SIMULTANEOUSLY RECORDED PREFRONTAL ENSEMBLES

9.1 MOTIVATION

Single-neuron studies into binocular rivalry and/or various other types of multistability have mainly reported modulation of activity in the earlier visual areas and other higher areas, such as the Inferotemporal cortex (ITC)[22,23,28,43,90]. Although they show reliable perceptual modulation, they do not address the activity of population of neurons monitored simultaneously. Moreover, one of the few studies into multistability in the prefrontal cortex only recorded single-neurons across days and during a binocular flash suppression task[62], which does not involve true spontaneous changes in perceptual content. Therefore, in this study, we wanted to understand if the content of consciousness can be reliably decoded from simultaneously recorded neuronal ensembles during spontaneous transitions.

9.2 METHODS

For the experimental methods, see chapter 7, section 7.2

For every unit, we calculated a preference index - d', by quantifying the strength of its selectivity during PA and BR trials during both the PA and BR trials. It was calculated as follows:

$$d' = \frac{\mu_S - \mu_N}{\sqrt{\frac{1}{2}\left(\sigma_S^2 + \sigma_N^2\right)}}$$

where, μs and μN refer to the average spiking response of a given unit during the presentation of its preferred (S – signal) and non-preferred stimulus (N – noise), calculated over a duration of 1000 milliseconds after a stimulus or a perceptual change. The difference between these two quantities is normalised by the variance in the response distributions.

For the decoding analysis, the Maximum Correlation Coefficient method was used as implemented in the Neural Decoding Toolbox[91]. To quote –

> *This CL object **(i.e. the algorithm)** learns a mean population vector (template) for each class from the training set (by averaging together the all training points within each class). The classifier is tested by calculated Pearson's correlation coefficient between a test point and the templates learned from the training set, and the class with the highest correlation value is returned as the predicted label. The decision values returned by the classifier are the correlation coefficients between all test points and all templates.*

9.3 RESULTS

We show here for the first time that single neurons and multi-unit activity in the ventrolateral prefrontal cortex reliably reflect the current perceptual state, i.e., the feature-selective neurons follow the perceived stimulus. This is seen in the typical divergence in the firing rate of two feature-selective neurons following both a spontaneous and a physical transition.
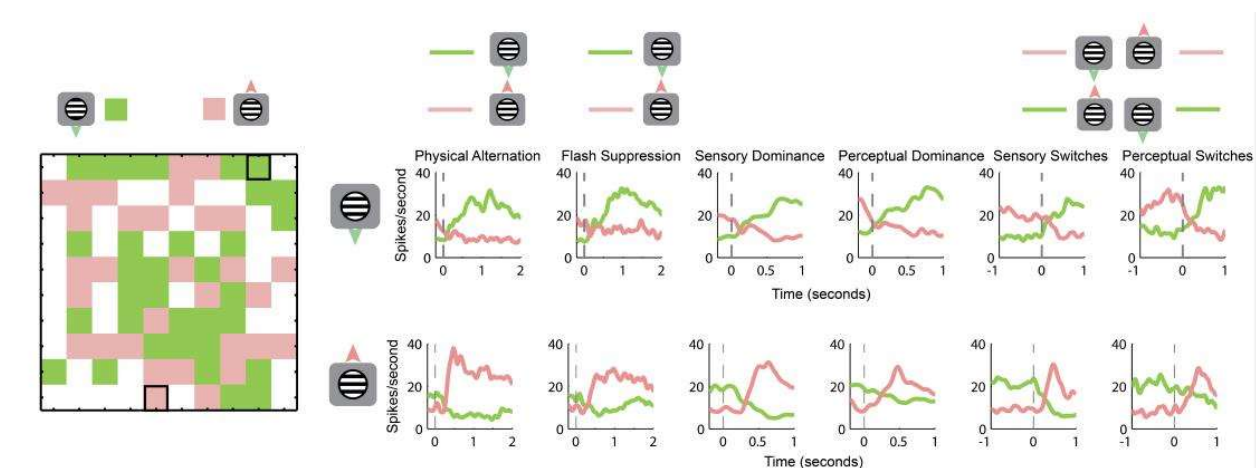
Figure 10 – Population activity of feature-selective ensembles.

Furthermore, these feature-selective neurons show strong modulation in their activity, computed as the d-prime metric.
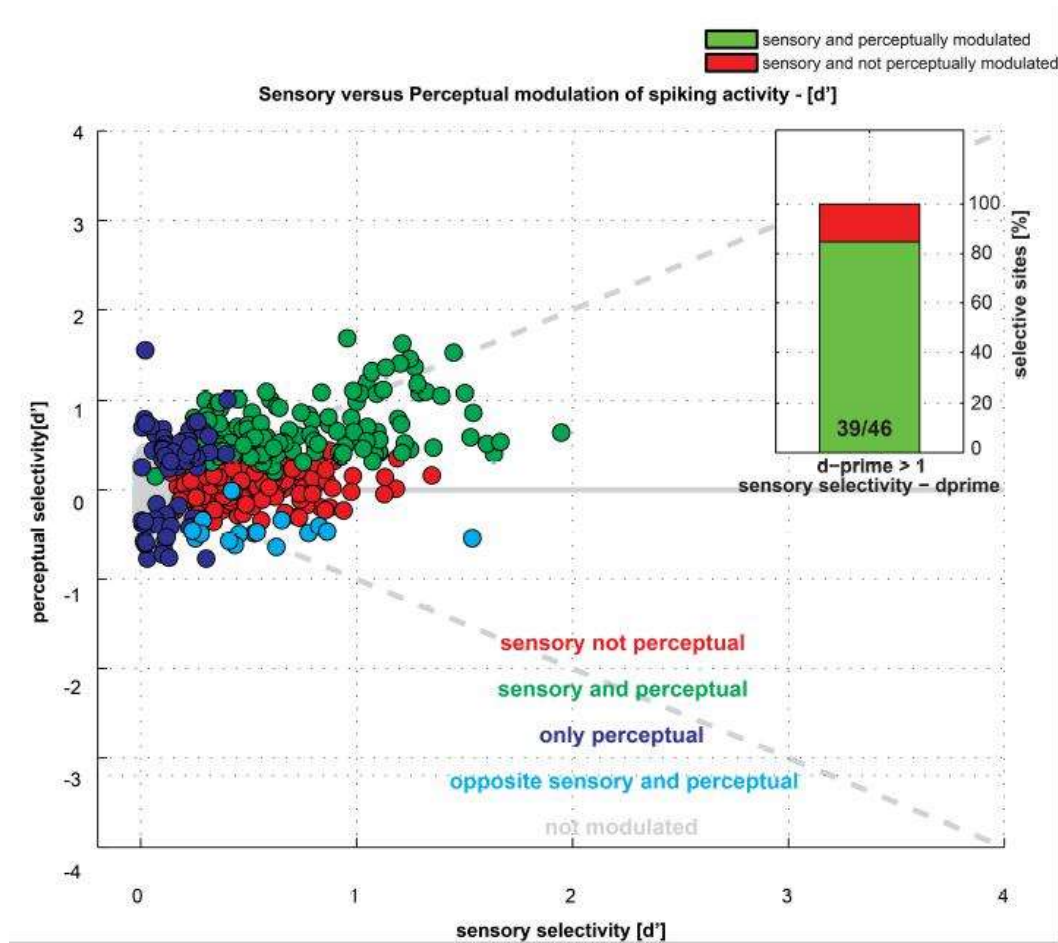
Figure 11 – Comparison of perceptual and sensory modulation using the d' metric.

Similar patterns are observed in the activity of simultaneously recorded neuronal populations. We also show that the content of consciousness can be robustly decoded from this activity and can be generalised across time, conditions, and units, with decoding accuracies between 80-95%. Finally, the use of a similar decoding approach on the eye-movement control experiments reveals no eye-movement confounds, pointing to the fact that the recorded neuronal activity, indeed, only reflects the content of visual consciousness and not the behavioural report (OKN).
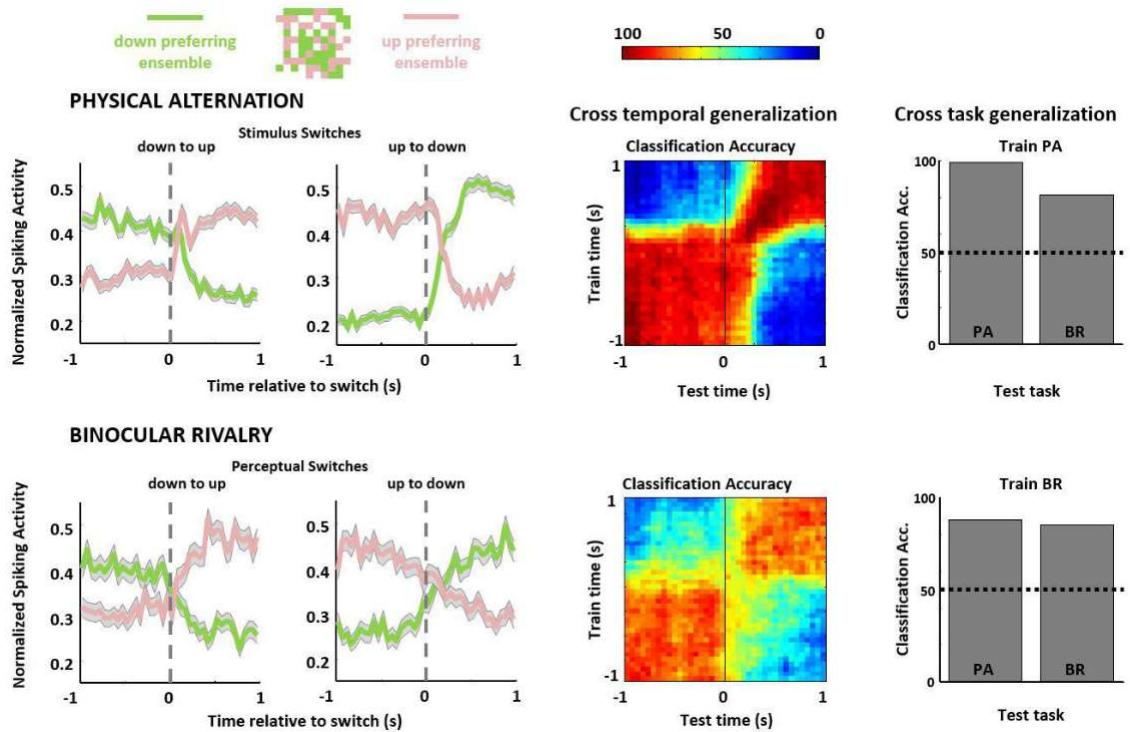
Figure 12 – Ensemble population activity and decoding accuracy

9.4 CONCLUSION

We show here for the first time that not only does the vlPFC reliably reflect the content of visual consciousness via the modulation of feature-selective neurons, this population activity can be used to robustly decode the content of visual consciousness. Most importantly, we show that the information contained within the activity of these neuronal ensembles are not eye-movement dependent; rather, they reliably reflect the actual stimulus content, pointing to the role of the PFC in maintaining and signalling the current state of conscious content.

10 NONMONOTONIC SPATIAL STRUCTURE OF INTERNEURONAL CORRELATIONS IN PREFRONTAL MICROCIRCUITS

10.1 MOTIVATION

The functional connectivity patterns of neuronal populations constrain the computational power and diversity of a given cortical patch[92,93]. The shape of correlated variability, computed as the mean spike-count correlations between neuronal pairs at a given separation between them, varies among different cortical regions[94–99]. This shape is defined by the type and density of horizontal connectivity between cortical columns. In the early visual areas, the strength of connectivity decays linearly as a function of distance[96,99]. However, because of the larger amount of horizontal differentiation and the pattern of distribution of specific neuronal types in the prefrontal cortex[100,101], the shape of this connectivity kernel is expected to be different and important in various prefrontal specific processes such as recurrent activity, persistence, etc. This study unravels the shape of functional connectivity in the ventrolateral prefrontal cortex.

10.2 METHODS

Two adult male macaques (Makkay and Dino) were implanted with a 10x10 Utah microelectrode array each. Short movie clips of 10s were shown to each monkey under anaesthesia, followed by a 10s inter-trial interval. Two further adult male macaques (A11 and H07) were also implanted with Utah arrays in the same region, i.e., the vlPFC and trained to fixate on a stimulus (moving grating in eight directions). Spikes were recorded and sorted offline. Spike count correlations were calculated as

$$c(r_i, r_j) = E[z_i z_j]$$

where Zi and Zj are the z-scored spike-counts in each trial for a single neuronal pair, and c is the Pearson's correlation coefficient. Tuning curves were also computed along with signal correlations.

10.3 RESULTS

We show for the first time, a non-monotonic structure of functional connectivity in the vlPFC, as opposed to a linearly decreasing structure over distance in the early visual areas. Correlations were strongest for proximal and distal pairs (almost equivalent), while they were the lowest for the medial pairs.
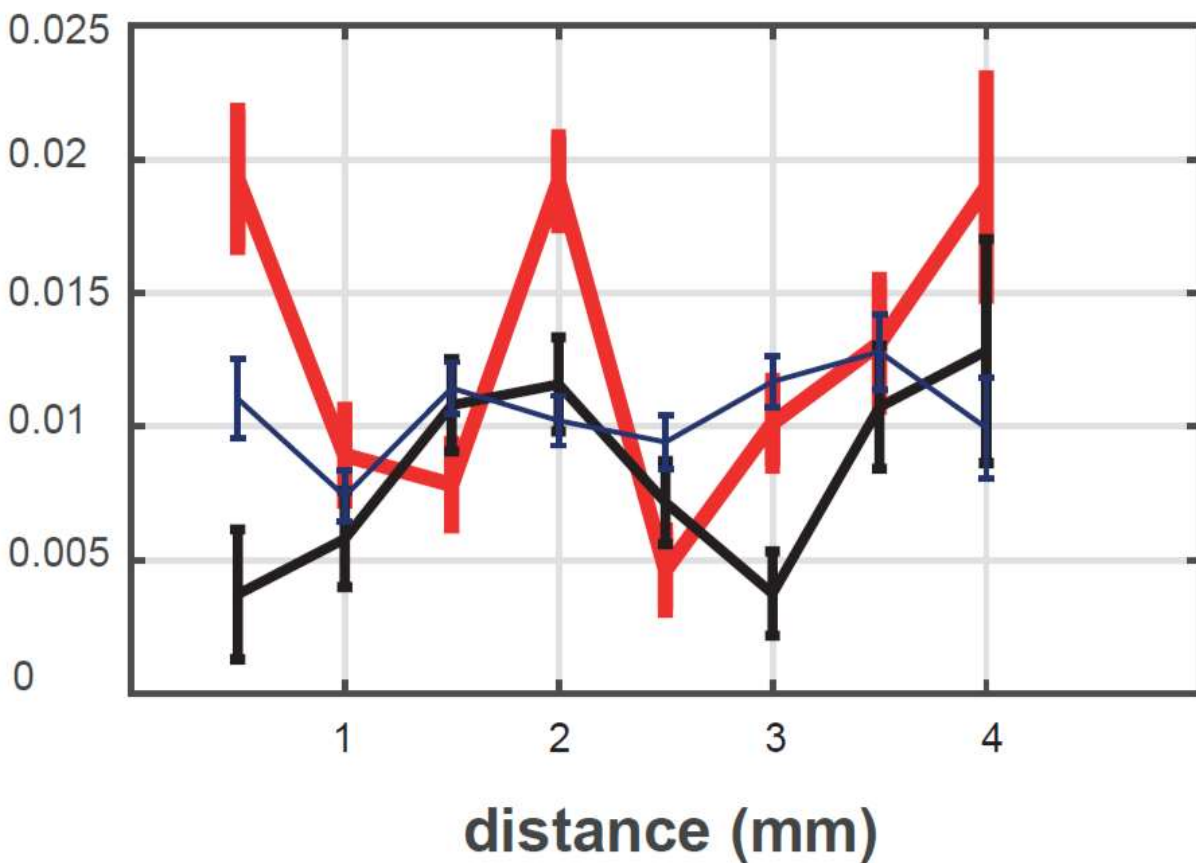
Figure 13 – Spatial structure of spike-count correlations during visual stimulation, inter-trial period and during resting-state (wakefulness).

This structure was observed during visual stimulation, both under anaesthesia and when awake. Furthermore, during the awake state, only the neuronal pairs with high signal correlation display a prominent non-monotonicity, pointing to the fact that functional engagement of neurons additionally determines the structure of correlated variability.
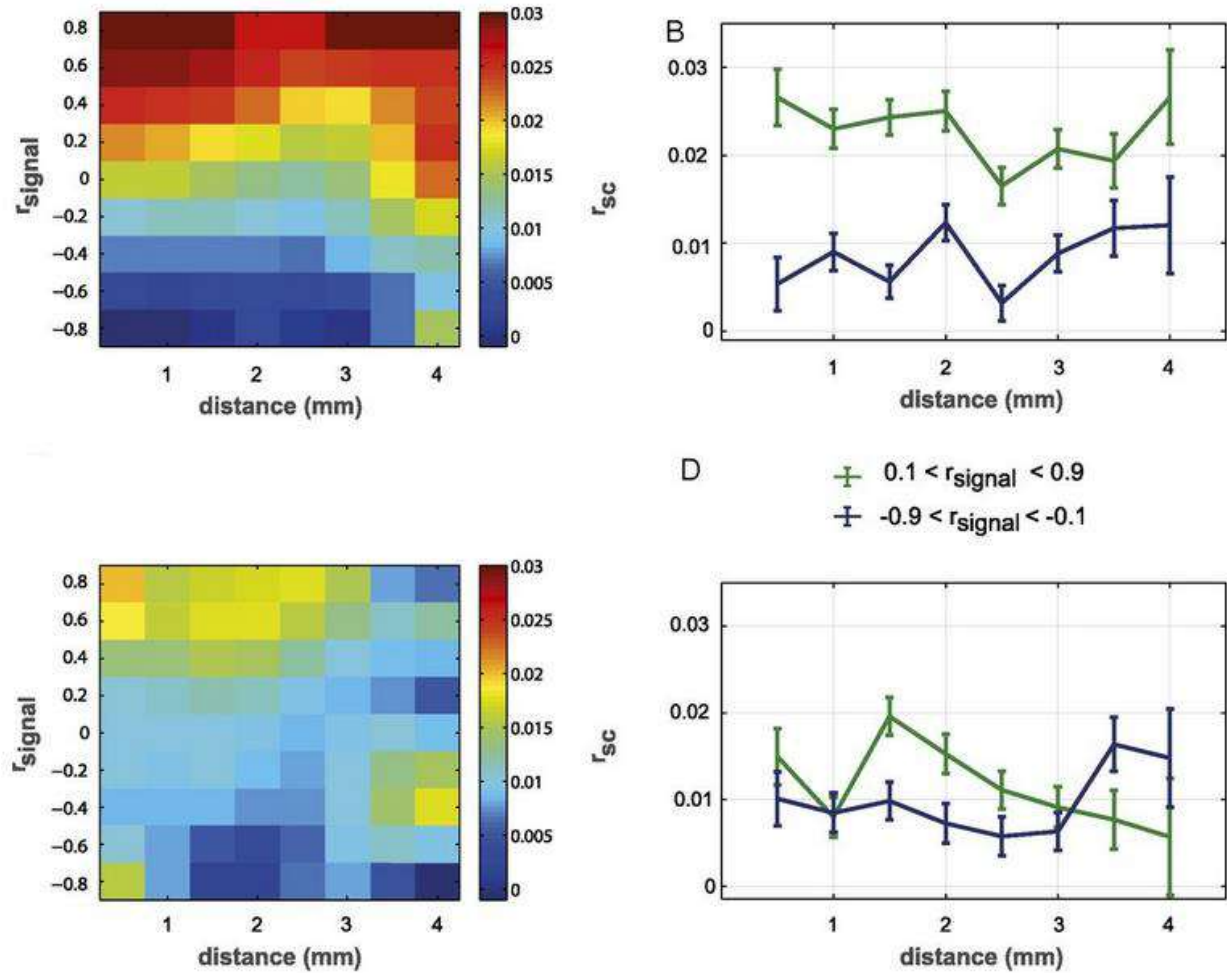
Figure 14 – Structure of noise-correlations in functionally similar (green) and dissimilar neurons (blue). (Top row – stimulation, bottom row – intertrial)

10.4 CONCLUSION

Our results demonstrate that the mesoscopic functional architecture of the vlPFC is fundamentally different compared to the early sensory areas such as the V1 and the V4. Correlated

variability in the vlPFC is spatially nonmonotonic and this shape results from the spatial pattern of correlations between neurons with similar functional properties. This non-monotonic functional connectivity kernel has profound implications in rethinking the nature and role of computations in higher-order areas that make possible a wide variety of cognitive phenomena.

11 DISCUSSION AND CONCLUSIONS

From our two studies on the neural dynamics of the disambiguation of rivalrous stimuli, it is clear that the frontal cortex cannot be dismissed as playing no role in resolving perceptual ambiguity or in refreshing the content of consciousness, which we define as a "switch" or a "transition" in the dominant percept. We show for the first time that there exist slow oscillatory and ongoing prefrontal states that strongly precede a spontaneous perceptual transition, when no physical report is elicited. Specifically, these slow oscillations operate as a gating-like mechanism; i.e., they must ramp up in amplitude as well as activate a threshold (sufficient) number of neuronal sites for a perceptual switch to occur. This may be realised akin to a *Bereitschaftspotential* or a readiness-potential which is commonly observed in the supplementary motor area (SMA) before a voluntary movement; indeed, it manifests before even the volitional awareness of wanting to make a movement[102–104].

Furthermore, it is known that the suppression of the ongoing and bursting beta activity reflects a decrease in active cortical processing[105] of states such as attention, planning and decision making[106,107]. A suppression of this activity removes the shielding of these cognitive states from interfering bottom-up sensory information. We suggest, therefore, that transient decreases in beta activity increase sensory information relay by controlling bottom-up sensory processing through top-down prior information[67,108]. This antagonistic suppression of the ongoing beta state by low-frequency bursts could indeed be akin, then, to the mechanics of rule-selective prefrontal ensembles that are coherent in the beta band with low-frequency activity inhibiting a rule that is about to be deselected[109], suggesting that the underlying prefrontal mechanism for consciousness and cognitive control might be the same. We propose that the intrinsically-generated prefrontal beta activity could reflect the prefrontal threshold that has been long hypothesised to control access to consciousness[110–113]. Most importantly, this top-down mechanism of perceptual reorganisation is fundamentally different from bottom-up mechanisms, proposing that competition between monocular neurons in primary visual cortex (V1) resolves perceptual ambiguity, as for e.g., neurons are only weakly modulated in the V1 as compared to the PFC, and most strikingly, there exist neurons that respond to both stimuli, i.e. monocular and

binocular neurons, with a significant percentage of them also responding to the unconscious stimulus[22,114].

If these oscillatory states are ongoing, that is, they happen all the time, they should also exist during resting state, i.e., when there is sensory deprivation (here specifically visual deprivation). Indeed, previous studies have shown that spontaneous cortical activity can attain various states during wakefulness, specifically in terms of mimicking sensory-driven activity[115–117]. We observed similar ongoing beta activity, occasionally suppressed by low-frequency bursts also during resting state recordings. Considering a sustained period of beta bursting to be analogous to the steady-state beta observed during stable dominance of a stimulus, the distribution of durations of these beta activity periods revealed a psychophysical-like Gamma distribution with a median duration nearly equal to the psychophysical distribution, thus strongly suggesting that the phenomenon of binocular rivalry, is emergent with complex hierarchical dynamics, which we hope to unravel in the future.

Finally, it is clear from the large percentage of perceptually modulated single-neurons showing clear stimulus preferences in the vlPFC, and the population activity of simultaneously-recorded ensembles, that, the PFC does indeed reflect the content of visual consciousness, thereby allowing us to reliably decode this content without making any prior assumptions on the nature and activity of these neurons. Taken together, our results show that not only is the prefrontal cortex a singnificant node in reflecting conscious content, but more importantly, that atleast some processes pertaining to state transitions in conscious percept are either localised or do indeed originate in this rich and mysterious area of the brain.

12 FUTURE OUTLOOK

Our studies on the functional organisation and phenomenology of visual consciousness of and in the frontal lobe have revealed hitherto unknown structures and mechanisms. Along with the recent study published by Gelbard-Sagiv and co-authors[63], our results strongly suggest the role of the frontal lobe and more specifically the fronto-parietal loop in accessing consciousness. Future studies must then ideally manipulate these discovered correlates to unequivocally answer the proximate question, i.e., the "How" question. One of the ways we plan to investigate these correlates is by micro-stimulation of feature-selective sites on the array, monitored online. We also wish to probe the surrounding cortical layers for their population activity using simultaneous multi-photon imaging which allows us to monitor large populations of neurons due to the resultant excitation of fluorophores. One major advantage is that using multi-photon microscopy along with cell-type specific dyes, we can monitor populations of neurons of our choice, be they excitatory or inhibitory neurons. Coupling these studies with tracer injections after explantation of the array, we can also investigate the extent of the contribution of the underlying anatomy and the imposed paradigm on the observed non-monotonic structure of functional connectivity in our data, and whether this indeed plays a role in stabilising the content of consciousness and its switching, in the prefrontal cortex.

I would like to end my dissertation with a more ambitious thought. The neural implementation of computational algorithms is not as simple as a collection or network of neurons playing specific bottom-up roles, be it in cognitive control or in sensory relay and object recognition. Predictive coding is one way of realising complex computations and convergence in neural networks along with minimising computational energy, time, and spatial resources. In a panel discussion, when I asked the speakers how cortical codes can be so simple as just a firing rate modulation, one of them said, and I'm paraphrasing; that stimulus, task, and other such information can be in states of superposition akin to a particle in quantum physics, while what you read out could be thought of as analogous to the quantum state collapse during observation. What if this higher-dimensional abstraction of information is happening in the subcortical regions in

massive parallel processing due to rich differentiation in these areas? These areas also have strong feedforward and feedback connections from higher cortical regions. Therefore, I hypothesise that the most optimal readout is being sent to the cortex to optimise report and behaviour. To test this, in the future, I would like to implant multiple microelectrode arrays along the dorsal pathway coupled with either laminar recordings or multi-photon investigation of deep subcortical structures, performed simultaneously, and analyse the wealth of data thus generated from within the Free Energy and Predictive Coding frameworks. This would be a monumental step towards understanding the incredible complexity and emergent phenomena that defines this wonderful and most mysterious organ that is the core of our very existence, the brain. Indeed, as Descartes famously said

"Cogito, ergo sum" (I think, therefore I am).

13 STATEMENT OF CONTRIBUTIONS

NB – An asterisk (*) indicates co-first-authorship.

13.1 THE ROLE OF THE OCCIPITAL CORTEX IN RESOLVING PERCEPTUAL AMBIGUITY

Grassi, P.; Schauer, G.; **Dwarakanath, A**.: The Role of the Occipital Cortex in Resolving Perceptual Ambiguity. Journal of Neuroscience 36 (41), S. 10508 - 10509 (2016)

P.G. initiated the article. P.G. wrote the first draft. G.S. and A.D. contributed in content, editing, discussions and finalizing the manuscript.

13.2 PREFRONTAL STATE FLUCTUATIONS CONTROL ACCESS TO CONSCIOUSNESS

Dwarakanath, A*.; Kapoor, V*.; Fedorov, LA.; Safavi, S.; Werner, J,: Panagiotaropoulos, TI.;Logothetis.: Prefrontal state fluctuations control access to consciousness. (in submission)

Conceptualisation: AD, VK, TIP (lead), NKL; Data curation: AD (lead), VK and JW; Formal analysis: AD (lead), VK, LAF; Funding acquisition: NKL; Investigation: AD (equal), VK (equal), TIP (supporting); Methodology: AD (equal), VK (equal), SS, (supporting), TIP (equal); Project administration: TIP; Resources: JW, NKL (lead); Software: AD (lead), VK, LAF, JW; Supervision: TIP; Visualisation: AD (lead), TIP (supporting); Writing - original draft: AD, TIP (lead); Writing - review & editing: AD, VK, LAF, SS, TIP, NKL (lead).

13.3 Decoding spontaneous changes in the content of consciousness from prefrontal ensembles

Kapoor, V*.; **Dwarakanath, A*.**; Safavi, S.; Werner, J.; Besserve, M.; Panagiotaropoulos, TI.; Logothetis, NK.: Decoding spontaneous changes in the content of consciousness from prefrontal ensembles (in submission)

Conceptualisation: VK, AD, TIP (lead), NKL; Data curation: AD (lead), VK and JW; Formal analysis: VK (lead), AD, SS, MB; Funding acquisition: NKL; Investigation: VK (equal), AD (equal), TIP (supporting); Methodology: VK (equal), AD (equal), SS (supporting), MB (supporting), TIP (equal); Project administration: TIP; Resources: JW, NKL (lead); Software: VK (lead), AD, SS, JW; Supervision: TIP; Visualisation: VK (lead), TIP (supporting); Writing - original draft: VK (lead), TIP (supporting); Writing - review & editing: VK, AD, SS, TIP, NKL (lead).

13.4 Nonmonotonic spatial structure of interneuronal correlations in prefrontal microcircuits

Safavi, S*.; **Dwarakanath, A*.**; Kapoor, V.; Werner, J.; Hatsopoulos, N.; Logothetis, N.; Panagiotaropoulos, T.: Nonmonotonic spatial structure of interneuronal correlations in prefrontal microcircuits. Proceedings of the National Academy of Sciences of the United States of America 115 (15), pp. E3539 - E3548 (2018)

N.K.L. and T.I.P. designed research; A.D., V.K., J.W., and T.I.P. performed research; N.G.H. and N.K.L. contributed new reagents/analytic tools; S.S., A.D., V.K., and T.I.P. analyzed data; and S.S., A.D., V.K., N.G.H., N.K.L., and T.I.P. wrote the paper.

13.5 TESTING THE PERCEPTUAL EQUIVALENCE HYPOTHESIS IN MENTAL ROTATION OF 3D STIMULI WITH VISUAL AND TACTILE INPUT

Caissie, A.; **Dwarakanath, A**.; Toussaint, L.: Testing the perceptual equivalence hypothesis in mental rotation of 3D stimuli with visual and tactile input. Experimental Brain Research 236 (3), pp. 881 - 896 (2018)

A.C. and L.T designed the research, A.C. collected the data. A.C. and A.D analysed the data. A.C wrote the first draft. A.C, A.D. and L.T edited and revised the manuscript.

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