

## RENATE RUTIKU

Refining the methodology  
for investigating the neural correlates  
of consciousness





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for investigating the neural correlates  
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## LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, further referred to by respective Roman numerals:

- I** Rutiku, R., Aru, J., & Bachmann, T. (2015). General markers of conscious visual perception and their timing. *Frontiers in Human Neuroscience* (submitted).
- II** Rutiku, R., Martin, M., Bachmann, T., & Aru, J. (2015). Does the P300 Reflect Conscious Perception Or Its Consequences? *Neuroscience*, 298, 180–189.
- III** Rutiku, R., Tulver, K., Aru, J., & Bachmann, T. (2015). Visual masking with frontally applied pre-stimulus TMS and its subject-specific neural correlates. *Behavioural Brain Research* (submitted).
- IV** Aru, J., Rutiku, R., Wibral, M., Singer, W., & Melloni, L. (2015). Early effects of previous experience on conscious perception. *Neuroscience of Consciousness* (submitted).
- V** Rutiku, R., Einberg, A., Imanaka, K., & Bachmann, T. (2013). The effect of task-irrelevant visual backgrounds on cortical alpha activity and TMS-evoked EEG responses. *European Journal of Neuroscience*, 38(12), 3768–3777.
- VI** Stamm, M., Aru, J., Rutiku, R., & Bachmann, T. (2015). Occipital long-interval paired pulse TMS leads to slow wave components in NREM sleep. *Consciousness and Cognition*, 35, 78–87.

The author of the present dissertation contributed to these publications as follows:

- In Study **I**: participated in developing the paradigm and stimulus set, conducted the experiments and data collection, carried out data analyses and wrote the manuscript as the main author.
- In Study **II**: participated in developing the paradigm, conducting the experiments and data collection, carried out data analyses and participated in writing the manuscript.
- In Study **III**: participated in developing the paradigm, conducting the experiments and data collection, carried out data analyses and wrote the manuscript as the main author.
- In Study **IV**: conducted the experiments and data collection, carried out data analyses and participated in writing the manuscript.
- In Study **V**: participated in developing the paradigm, conducting the experiments and data collection, carried out data analyses and wrote the manuscript as the main author.
- In Study **VI**: participated in refinement of the study concept, carrying out data analyses and writing the manuscript.

Principal aims of the studies are to:

- Study I: identify markers of conscious visual perception that generalize across different stimuli and are reliable enough within one study.
- Study II: test if the P300 component could rather mark a consequence of conscious visual perception related to working memory processes.
- Study III: investigate whether pre-stimulus TMS masking of visual targets is also possible through stimulation of frontal areas of the brain and identify the neural markers of this effect.
- Study IV: investigate the specific behavioral and neural effect of prior knowledge on conscious visual perception by concurrently controlling for the well-known effect of sensory evidence.
- Study V: determine whether consciously perceived task-irrelevant background images can be distinguished on the basis of neural responses to TMS perturbation during prolonged perception.
- Study VI: investigate whether it is possible to induce sleep slow waves (a well-known marker for the loss of consciousness during sleep) also from the early visual cortex if a long-interval paired pulse TMS regime is employed.

# INTRODUCTION

The perceptual capacity of the brain is amazing. The most puzzling part of it is, however, that the objective neurobiological processes on which this capacity is founded are capable of creating a conscious experience of what we perceive. This ability is indeed so puzzling that a precise definition of consciousness is hard or even unreasonable to formulate at this point (Crick & Koch, 1990). In the most general sense “Consciousness consists of those states of sentience, or feeling, or awareness, which begin in the morning when we awake from a dreamless sleep and continue throughout the day until we fall into a coma or die or fall asleep again or otherwise become unconscious” (Searle, 1997).

The present thesis is concerned with our immediate and subjective sensory experience that tends to accompany our interactions with the world and which could be described as the basic, “entry level” consciousness exemplified by the phenomena of sensation and perception (Block, 1995). Despite its seemingly straightforward immediate appearance, conscious perception has remained largely a mystery for fundamental sciences studying consciousness. The present work aspires to further our understanding of the neural basis of conscious perception by improving the experimental paradigms, by using more sensitive analysis methods and by considering other possible related phenomena such as concurrent mental states accompanying consciousness. The following overview is set to show how the present approach is related to the currently important directions in the field of scientific studies of consciousness and how the experimental and theoretical work carried out in the context of the present thesis contributes to them.

Because vision is by far the most dominant of human (and also primate) senses most research on conscious perception has concentrated on the visual modality. This is also true for the work at hand. Therefore, most of the following discourse and the corresponding examples will be about conscious *visual* perception. One should nevertheless keep in mind that the phenomenon of consciousness does not only encompass our ability to see and the long-term goal of the study of consciousness is to unveil the neural basis of any kind of conscious experience.

Besides the fundamental importance of this question it also is clinically relevant. Understanding how consciousness arises in the brain would help to better identify whether or not a patient is conscious, advance anesthetic procedures and techniques or even treat disorders such as diseases and traumas accompanied by coma and vegetative state.



## **I. Toward the neural basis of consciousness**

### **I.1 The neural correlates of consciousness (NCC)**

How to study the neural basis of a naturally occurring phenomenon if there is no objective way to observe this phenomenon directly? This is the biggest problem facing the neuroscience of consciousness today. As consciousness is, first and foremost hallmarked by a subjective quality of experience the only waterproof way to really know “from outside” if an event was consciously experienced or not is to ask the respective individual to report his/her introspective experience (Baars, 1988). Ideally, however, we would like to have objectively observable neural indicators of whether the event was indeed consciously perceived. The most common strategy to study consciousness to date is therefore to compare the neural activity that accompanies the reported conscious experience of a well-defined event to neural activity when the same event was not consciously experienced. The goal of such a contrastive approach is to find markers for the neural correlates of consciousness (NCC) – the “minimal set of neural events jointly sufficient for a specific conscious experience” (Koch, 2004). The hope is that once such objectively observable markers (i.e. macroscopic measurements reflecting the critical neural events) are found one can proceed to studying the underlying NCC and ultimately the actual mechanism that are indexed by these NCC.

### **I.2 The problem with the NCC**

The simple and elegant NCC concept outlined above has been fruitful in many ways. There are now several candidate markers of NCC that have been identified in a plethora of studies (e.g. Koivisto & Revonsuo, 2010; see also **Studies I and II** for a more detailed discussion). Somewhat more worrisome is, however, that no consensus about the most important markers of NCC has yet emerged. Some studies have found that the markers of NCC occur relatively late and are related to large-scale activity in fronto-parietal networks (e.g. Del Cul et al., 2007). Others have found much earlier markers arising solely in the early visual cortex (e.g. Pins & ffytche, 2003), and recently, mid-latency markers of NCC in occipito-temporal networks have received the most attention (Koivisto & Revonsuo, 2010).

It has been proposed that one reason for the contradictory empirical results may be related to the method of identifying the markers of NCC – the contrastive analysis (Overgaard, 2004; Bachmann, 2009; Aru et al., 2012b; de Graaf et al., 2012). By contrasting the neural activity in conditions with conscious perception to conditions without conscious perception only those markers should be identified that are uniquely present or reliably more strongly present when conscious perception occurred. However, the markers of NCC may not constitute the only significant differences in this situation. Depending on the study at hand, neural prerequisites (NCC-pr) and neural consequences (NCC-co) may also vary systematically between conditions with and without

consciousness. Consequently, by conducting a contrastive analysis these additional processes may be misclassified as NCC proper.

For example, imagine a very boring and tedious experiment where the perception of faint stimuli has to be rated (NB! This is a quite typical description of NCC experiments). Due to random fluctuations in attention some faint stimuli may benefit relatively more from the attentional enhancement than others thus leading to an increased probability that the former stimuli are perceived consciously. Now, by conducting a contrastive analysis not only the NCC but also the neural correlates of attention will be present (or relatively more strongly present) in the condition with conscious perception. Consequently, they will also be reflected in the results of the contrastive analysis and get misclassified as NCC proper (Aru et al., 2012b; De Graaf et al., 2012). Note that although attention and consciousness are regarded as one and the same phenomenon by some researchers we do not share this view (for a relevant discussion see Bachmann, 2006, 2011; Koch & Tsuchiya, 2007; Wyart & Tallon-Baudry, 2008; Aru & Bachmann, 2015). Strong arguments against the view that attention and consciousness are equivalent come from the experiments showing that selective attention disturbs target consciousness (Bachmann & Murd, 2010; Murd & Bachmann, 2011).

Several theories of consciousness put a lot of emphasis on integration of neural activity taking place in mutually distant brain locations (Dehaene & Changeux, 2011; Tononi & Koch, 2008; Melloni & Singer, 2010). Thus, consciousness is thought by many to be a more global integration process – it is intimately related to a multitude of other processes participating in mental activity, whether conscious or unconscious. It is no wonder then that the 3 types of NCC (NCC-pr/NCC proper/NCC-co) have proven to be quite difficult to delineate in practice.

### **I.3 Possible solutions to the NCC problem**

Although it has been realized for a while now that the contrastive method has its pitfalls when applied to the study of the markers of NCC (Overgaard, 2004; Bachmann, 2009; Aru et al., 2012b; de Graaf et al., 2012) no definite solution to the problem has yet emerged (Aru et al., 2015). Many studies have tried to delineate conscious perception from some other parallel process such as attention or working memory, but since it is never possible to argue that all NCC-pr/NCC-co have been accounted for it is also not possible to argue that the identified differences really are the markers of NCC proper.

Due to this unfortunate methodological situation the NCC concept seems to have fallen out of favor lately. One can nevertheless argue that no better alternative to the NCC concept currently exists. Until we do not understand and precisely measure the brain and its processes better we can only use approximations of the mechanism of consciousness in the form of markers and correlates – be it properties of single neurons or larger networks. The idea is thus to use “the ability to predict as a surrogate for understanding” (Devor et al.,

2013). In order to do that we must continue to look for more reliable neural activity markers that are exclusively present in conditions with conscious perception compared to conditions without conscious perception (i.e. the markers of NCC). We must thus look for alternatives to the problematic contrastive approach, but also for ways to improve the contrastive approach itself.

These goals have been realized in the present work by adopting the following rationales:

**Rationales:**

- 1) More refined experimental paradigms are needed to control for or investigate possible NCC-pr/NCC-co. (**Studies I, II, III, and IV**)
- 2) The stimuli used in typical paradigms are too restrictive and artificial. This may distort or bias the results and pose an obstacle for revealing the general markers of consciousness invariant to the narrow range of stimulus contents. (**Studies I, IV and V**)
- 3) More attention should be given to the variability in results and how it can be explained. (**Studies I, III and IV**)
- 4) The ongoing state of the brain must be taken into account when investigating the neural markers of consciousness as a response to natural and artificial perturbations of the brain. (**Studies III, V and VI**)

## **2. Reliability and stability of NCC**

As outlined in the previous chapter the contrastive method which is typically used to identify the markers of NCC has its pitfalls. If conditions with and without conscious perception are contrasted NCC-pr and/or NCC-co may be misclassified as NCC proper. Note that these accompanying processes need not be the same in all studies, but may depend on the specifics of the applied paradigm and stimulus material (Aru et al., 2012b). For example, the N170 component may be a marker of NCC-pr or even NCC proper exclusively for faces (Navajas et al., 2013; see also **Rationale 2**). This makes the different NCC studies inherently difficult to compare since it is unclear to what extent their results should overlap or whether they should have a common denominator at all (Dehaene & Changeux, 2011). However, it has been the underlying assumption from the very beginning that “/.../ all the different aspects of consciousness /.../ employ a basic common mechanism or perhaps a few such mechanisms.” (Crick & Koch, 1990). Thus, it is not unreasonable to assume that all the different NCC paradigms could in principle share a common marker. Again, the reason why so many paradigms do not share a common NCC marker may have to do with the contrastive fallacy.

Namely, the contrastive analysis may not only be problematic between studies (misclassification of NCC-pr/NCC-co as NCC proper), but also within studies. The identified markers of NCC may not be reliable nor stable if only one specific paradigm is considered (see Introduction of **Study I** for a longer

description of this problem). It has been long recognized that evoked neural responses to a repeated stimulus exhibit large variability. Arieli et al. (1996) demonstrated that this variability in cortical evoked activity is related to the fluctuating initial state ante target stimulus. However, as the authors themselves note the prominent ongoing background activity continues to change while the deterministic evoked response unfolds. Thus, the signal is composed of non-stationary ongoing activity and a possibly variable evoked response over trials. Of course it would be nice if we could assume that the conditions with and without conscious perception are both equally variable (i.e., effectively invariant) in terms of these two signal components within one study, but are they?

Interestingly and related to this issue, a recent advance in the field has been accomplished by Schurger et al. (2015) who show that activity in the unconscious condition is more variable. Thus, the conscious condition is characterized by more stability within and across trials (although see also Solovey et al., 2015). In hindsight, a case may even be made for the claim that many if not all of the measures of conscious perception depend on higher stability in the “seen” condition (consider synchrony, for example; Melloni et al., 2007). But if stability really is a property of conscious perception then how does this property relate to more typical markers of NCC within one study?

In case of event-related potentials (ERPs) it would mean that the ERP estimate of the unconscious condition is more variable than the ERP estimate of the conscious condition. It seems to the author of this thesis that too little attention is usually given to what is happening in the unconscious condition in the experiments that have adopted the contrastive analysis. When people think and talk about the markers of NCC usually they only consider what is happening in the conscious condition. But by using the contrastive analysis what is identified as the markers of NCC is actually a *difference* between two conditions. If one condition is more variable than the other then this will also be reflected in the difference. These circumstances will definitely affect the time at which the difference starts to become reliable. In the worst case scenario they may even hide the markers of NCC from the contrastive analysis altogether.

Thus, **Study I** was designed to investigate how much the markers of NCC vary when only the data from one experiment are considered. The goal was to test if it is possible to find reliable and stable estimates for NCC markers and their timing despite the pitfalls of the contrastive analysis. At this point we leave open the question of whether conscious perception emerges at once as a step function or gradually (Bachmann, 2000; 2013). In any case there is a moment or epoch of time when the initial change in the processes underlying the conscious percept takes place.

First, we wanted to create a paradigm that would be more general in terms of stimulus content and thus more clean in terms of the contrastive analysis (see **Rationales 1** and **2**). We presented a heterogeneous stimulus set at threshold contrast to reduce the role of visual categorical restriction. This also eliminated the confound of stimulus predictability as it is known that the latency of NCC markers may shift as much as 100 ms when stimuli become predictable

(Melloni et al., 2011). By averaging over trials where many different stimuli were presented we obtained more general markers of conscious visual perception (gmNCC) associated with seeing something at all (with narrow specificity dissolved) as opposed to the markers of NCC obtained when seeing one specific thing or a small set belonging to a restricted category. We then concentrated on the variability of these gmNCC (see **Rationale 3**) by repeatedly sampling from the pool of all available trials and thus creating 100 different but objectively (in terms of stimulus content) completely identical subsets of trials. To be abundantly clear, these subsets were always identical for the conditions with and without conscious perception and also for each of the 100 different subsets altogether, but at the same time avoiding the narrow class and exemplar specificity of stimuli so characteristic to the prevailing majority of studies so far. We then performed a contrastive analysis on each of the 100 matched subsets of trials with and without conscious perception separately. We recorded which ERP components differed between these two conditions and at what time the differences begun to arise.

First of all, the results suggest two quite reliable gmNCC for this study. The most prominent marker was the P300. This component was significant regardless of which subset of the data was considered. Another marker was the N200. This component reliably differentiated between the conditions in 81% of the individual contrastive analyses. Both components are well known from previous literature and have consistently been associated with conscious visual perception (Koivisto & Revonsuo, 2010). However, not all studies have found both markers. Because we observed that the markers of NCC (N200 in this case) can indeed be hidden from the results of a contrastive analysis depending on which subset of data is considered it is possible that other studies have missed some markers of NCC as well. Thus, due to the pitfalls of the contrastive method NCC markers are not always reliable even within one paradigm.

We also analyzed the variability in the onset timing of gmNCC, i.e., the time at which significant differences started to occur. Onset latency varied a lot from one subset to another even if noise/possibly unrelated ongoing activity was removed from the single trials to improve the condition specific ERP estimates. The mean onset latency of P300 was observed 232 ms after visual stimulus onset, but this onset ranged from 151–268 ms, i.e., varied almost over 100 ms depending on the included data. The mean onset latency of N200 was 208 ms, but it again varied over several tens of ms (191–232 ms). By analyzing single trial parameters (peak amplitude, peak latency, peak latency variance) during the range of observed onset latencies we show that it is first and foremost the fluctuating amplitude in the condition without conscious perception that determined when differences between conditions become evident – in other words, the *not* conscious condition substantially determines when the markers of NCC occur. These results thus demonstrate that stability may indeed differ between conditions and an increase in the stability of evoked responses may be a hallmark of conscious perception.

To summarize, in **Study I** we capitalized on a heterogeneous stimulus set and variability analysis to find out which markers of NCC are general across stimuli (**Rationales 2**) and reliable enough within one study despite the pitfalls of the contrastive method (**Rationale 1**). Results indicate that N200 and P300 are the two ERP components that satisfy these criteria. However, the results also exemplify the extent of the contrastive fallacy by showing how unstable the resulting NCC markers can be (possibly due to increased instability in the unseen condition). This variability within a single study cannot be taken lightly or discarded as measurement imprecision because the validity of the resulting conclusions may heavily depend on it (**Rationale 3**). Future research should thus be more aware of possible pitfalls of the contrastive method and try to find appropriate ways to estimate their extent (for example, see Railo et al. (2015) for an original approach).

### 3. Is P300 a NCC-co?

**Study I** indicates that N200 and P300 are the two candidate markers of NCC that generalize across different stimuli and are reliable enough within one study. However, it does not conclusively answer the question whether these components actually mark the NCC proper. Although we tried to avoid stimulus type specific NCC-pr/NCC-co that does not mean that there may not exist some general processes that almost always accompany the NCC proper. As already noted in Chapter 1.2 consciousness is often hypothesized to be intimately related to a multitude of other processes participating in mental activity. This makes it very difficult to tear the different subtypes of NCC markers apart in practice. Consequently, we also cannot exclude the possibility that one or even both of the identified gmNCC are actually not markers of NCC proper.

Particularly the notion that P300 is a marker of NCC proper has been criticized. Although it is the centerpiece of one of the best known theories of consciousness (the global neuronal workspace theory; Dehaene et al., 2006; Dehaene and Changeux, 2011; Dehaene et al., 2014) this component is classically known as a marker of working memory processes (Polich, 2007; 2012; but see also O'Connell et al., 2012; Kelly & O'Connell, 2013; Verleger et al., 2005; 2014). Indeed, recent research by Pitts et al. (2014a,b) and Shafto and Pitts (2015) has stirred up the debate about P300 by showing that it only occurs if the consciously perceived stimuli are also task-relevant (which was the case in **Study I**). Thus, it is possible that P300 rather reflects an update in working memory content insensitive to whether the target stimulus is conscious or unconscious.

To arrive at a better understanding of the role of P300 we conducted **Study II** to specifically test if P300 could mark a consequence of conscious perception, i.e., we tried to delineate it from the markers of NCC proper. Our reasoning was as follows. The typical perceptual tasks in consciousness research are quite demanding. Subjects often report that the stimuli are very



hard and ambiguous to perceive. Thus, trials with more or less clear perception might constitute relatively rare events. This is exactly the kind of situation that leads to the classic P300 response (Donchin, 1981), because it supposedly elicits an updating of the mental model or “schema” of the stimulus context in working memory (Polich, 2007; 2012). Furthermore, in most studies (e.g. Del Cul et al., 2007) several different stimuli are presented in a random order and subjects are required to perform some kind of discrimination task to objectively assess whether they really perceived the stimulus. This also poses additional load on working memory involvement. We designed **Study II** to avoid these possible confounds in order to test whether P300 still reflects conscious perception (**Rationale 1**).

In many ways the approach adopted in **Study II** was opposite to the approach of **Study I**, thus complementing it. First, we tried to make the perceptual events and stimuli in **Study II** completely predictable. Only one stimulus was presented on each target-present trial (exceptions were a few catch trials without a stimulus) and subjects were informed about this fact. Furthermore, the contrast of the target stimulus (a gray @ sign) was carefully adjusted to make sure that subjects would consciously perceive the target stimulus on the majority of trials (75%). No discrimination task was used. Subjects only had to report whether they perceived the stimulus or not. Finally, in an attempt to replicate the results of Pitts et al. (2014a,b) and Shafto and Pitts (2015) an additional counting task was introduced. Subjects had to count either the trials where the target stimulus was seen or the trials where the target stimulus remained unseen. These tasks were administered in alternating experimental blocks. If P300 indeed rather reflects the consequences of NCC (e.g., working memory update possibly depending on task relevance) then one would expect a relatively more pronounced P300 in the condition without conscious perception – especially when the unseen trials are counted.

Despite the above described theoretical considerations results did not confirm our expectations. P300 was relatively more pronounced for all seen conditions. The counting task did not have any systematic effect on the P300 amplitude as well. Thus, in **Study II** P300 must be considered as one seemingly reliable marker of NCC. Nevertheless, P300 was not the only NCC marker in this study. Another component – the N200 – also reliably distinguished between the conditions with and without conscious perception irrespective of the counting condition.

While **Study II** did not succeed in disassociating P300 from the candidate markers of NCC proper it must be recognized that this may also have hinged on several limitations of the experimental paradigm. Most importantly, we may not have achieved a sufficient relief of working memory demands which could have caused the results. P300 may have also indexed some other NCC-co in the adopted paradigm which was not taken into account. However, although this experiment was conducted specifically to study the P300 the same considerations also hold for the N200. Even if N200 peaked earlier than P300 this alone does not make it a more trustworthy candidate marker of NCC proper. For

example, N200 may be associated with attentional processes and not the NCC proper.

The above described results and discussion make it clear how hard it is to delineate the NCC-co from the NCC proper in practice. Obviously, further studies and more intricate paradigms are needed to test the role of P300 as well as N200 (**Rationale 1**). But keeping in mind that many studies have been conducted already that find very similar results (see **Study I**, for example) it may also turn out that both N200 and P300 are indeed markers of NCC proper and that they generalize over different stimuli and recording conditions (provided that the contrastive fallacy has been avoided). There persists a silent understanding in the field that only one ERP component can constitute a marker of NCC proper, but this must not necessarily be the case. According to the microgenetic description (Bachmann, 2000), conscious perception may evolve over different stages. The initial sensory aspect of perception may be established in an earlier fast stage. A more working memory based experience of stimuli may arise at a somewhat slower stage. Similar notions have also been proposed by several other researchers (e.g. Navajas et al., 2014).

#### 4. Possible network effects on NCC

In **Study II** we investigated possible NCC-co. But in order to get closer to the markers of NCC proper we also have to understand which processes are leading up to conscious perception as its prerequisites. As noted in Chapter 2, ongoing activity as a consequence of unperturbed spontaneous brain processes is often times as prominent as are evoked responses (Arieli et al., 1996). But is this ongoing activity also functionally relevant for upcoming stimulus processing? This seems to be in fact the case. Pre-stimulus activity – and in particular alpha oscillations in occipito-parietal cortices – can codetermine subsequent visual perception. For example, lower pre-stimulus alpha power is associated with increased performance on a difficult visual discrimination task (van Dijk et al., 2008). Equivalent results have also been reported for phosphene perceptions as a result of primary visual cortex (V1) perturbations by transcranial magnetic stimulation (TMS) (e.g. Romei et al., 2008). Currently it is a widely accepted view that initial information processing is in part dependent on the local pre-stimulus state of early sensory areas.

However, not only the local states of early sensory-perceptual encoding sites contribute to the processing of stimuli. For example, in visual masking of the target stimuli non-specific reticulo-thalamo-cortical modulation has long been argued to be critical for or at least instrumental in modifying conscious perception (Bachmann, 1994). Indeed, recent research demonstrates that more global network states may be just as important for upcoming stimulus processing as is local activity in sensory cortices (Weisz et al., 2014; Leonardelli et al., 2015; Sadaghiani et al., 2015; Godwin et al., 2015; Nierhaus et al., 2015). Thus, it is also important to understand these ongoing more general processes



and the state of functionally relevant networks because they may constitute critical NCC-pr (see **Rationales 1** and **4**). Importantly, many of these systems may work in a similar way irrespective of the specific stimulus contents.

Pre-stimulus masking with TMS offers a perfect setting to study the above described network phenomena. Similar to paracontrast masking, pre-stimulus masking with TMS is achieved by introducing a disruptive signal prior to the onset of a visual target stimulus (e.g. Corthout et al. 1999a,b). Unlike modal masking, however, the disruption comes from the precisely timed TMS pulse and the processes induced by TMS are unspecific to the content of modal stimulation. Thus, it is possible to target the underlying processes more specifically in time and space at the same time leaving content related specificity of processing exclusively to the modal target signals.

Previous successful pre-stimulus masking studies have directed the TMS pulse to the early visual cortex (e.g. de Graaf et al., 2011a,b; Jacobs et al., 2012, 2014; but see also Grosbras & Paus, 2003). Although non-specific by itself, this perturbation is directed right at the early functional areas specialized for visual contentful processing of the modal target stimuli and for which the importance of local pre-stimulus states has been demonstrated (see above). However, if general network states are as relevant as local activity in the early visual cortex then it should be possible to achieve a similar masking effect when TMS is targeted to other, non-visual areas located far from the visual modal cortex. To test this possibility **Study III** was carried out.

In this study participants solved a simple visual discrimination task. A brief light gray Landolt square was presented on each trial. First, subjects had to report on which side of the square the gap was located (objective task) and second, how well they perceived the gap on a 4 point scale ranging from not at all to clearly visible (subjective task). Importantly, in this study TMS or SHAM stimulation (tilted coil) was not targeted at the early visual cortex but at the right frontal cortex and a single pulse was given either 140 or 60 ms before stimulus onset or 20 ms after. Based on previous literature we expected to see the masking effect specifically in the -60 ms stimulus onset asynchrony (SOA) condition (e.g. Jacobs et al., 2012).

Results show that TMS to the frontal cortex indeed disrupted perception specifically in the -60 ms SOA condition with real TMS. This effect was most clear for the objective discrimination performance. Similar, albeit a much weaker effect was also evident for the subjective visibility rating. However, for both measures the presence and extent of the masking effect was highly variable over subjects. Some subjects exhibited a big drop in performance while others did not exhibit it at all. In order to study the neural correlates of the frontal masking effect we took advantage of this variability to look for connections between behavioral outcomes and brain responses (**Rationale 3**).

We identified the peak latencies of two TMS-evoked components (N100 and P270) and one visually evoked component (N200) from the ERPs of each subject separately and investigated whether they can account for how much individual performance dropped in the -60 ms SOA condition with real TMS

compared to SHAM stimulation. Because the study was initially conceived for the investigation of NCC-pr we were expecting to find very early effects – perhaps related to the TMS-evoked N100 component. The actual results were more surprising, however. By far the biggest portion of variability in objective discrimination results was explained by individual peak latencies of the late TMS-evoked P270 component (up to 45%). In contrast, peak latencies of the TMS-evoked N100 component did not explain any additional variability. Although not significant – peak latencies of the visually evoked N200 component did also seem to account for a little bit of variability in objective discrimination results over and above the P270 component. This is interesting because these two components indeed overlap specifically in the critical -60 ms SOA condition. However, mean amplitude of N200 did not seem to be modulated by this overlap. Mean amplitude of N200 was only modulated by subjective visibility ratings. On the other hand, none of the subject-specific peak latencies could explain the extent of individual changes in subjective visibility ratings in response to TMS at -60 ms SOA.

The strong correlation between the late TMS-evoked P270 component and the behavioral drop in objective discrimination performance indicates that the masking effect was not caused exclusively by a disruption of early visual processing that would clearly constitute a NCC-pr. Rather it seems that the unfolding neural response to TMS interacts critically with task-related processing around 200 ms after visual stimulus onset. Because the N200 component itself remained unaffected by TMS it is likely that the masking effect was not caused by disruption of the kind of visual processing marked by N200 at all. Instead the interference seems to have occurred with processes *temporally* coinciding with the visual N200, but not *reflected* in N200 itself. This conclusion is also strengthened by the fact that subjective visibility ratings did not decrease to the same extent as objective discrimination performance and no relationship between the subjective visibility ratings and the P270 component was found. Thus, one possible interpretation is that late TMS-evoked activity interfered with the use of perceptual information at higher cognitive levels (e.g. decision processes) or with the broadcasting of said perceptual information. Note that this interpretation is nevertheless compatible with the above proposed role of more global network states for conscious perception.

But how do the above described results contribute to our understanding of the NCC which is the main topic of the present theses? Several aspects confirm the importance of N200 as a marker of conscious visual perception (see also **Studies I and II**). First, N200 amplitude was higher when subjects experienced the target stimulus more clearly. Second, the objective masking effect was strongest when a late TMS component overlapped with the N200. However, the second result also poses several problems. For example, it is unclear whether NCC-pr/NCC proper/NCC-co were affected or whether this effect is related to the NCC at all. Because the effect was specific for objective discrimination performance it may constitute an instance of dissociation between objective task performance and subjective conscious perception (see also Rounis et al., 2010).

Thus, the employed paradigm could prove to be very useful for delineating the 3 types of NCC in the future (see also **Rationale 1**). After all, the N200 may index many other parallel processes in addition to the NCC as well and therefore – despite the conspicuous alignment of P270 and N200 – it is still unclear which process was affected exactly. Taken together, the results of **Study III** may illustrate how NCC can in principle overlap in time with NCC-pr, NCC-co or even with task-relevant processes that are unrelated to any of the 3 types of NCC (Aru et al. 2015; see also Bachmann (2015) on the uncertainties of studying brain-imaging markers of consciousness).

In any case, following **Rationale 3** we demonstrate that it is possible to exploit the variability in both behavior and neural responses to better study the critical processes underlying conscious visual perception. This is a step forward from the traditional ways of contrastive analysis. Also, following **Rationale 4** we show that it is important to understand what is going on in a larger network of task-related areas concurrently with the NCC in order to move toward a more precise and informed description of the NCC and the markers thereof.

## 5. Predictions and the NCC

As already mentioned above (see Chapter 2), predictions about upcoming stimuli have a systematic effect on subsequent neural responses. Furthermore, neural responses will be at least in part different depending on the stimulus material. **Study I** was designed to overcome these confounding factors, but now we turn to these topics in more detail in order to study their influence on conscious perception and on the related neural processes directly.

The information from the retina is ambiguous and noisy. Thus, according to the currently prevalent belief it is necessary to complement sensory information by internally driven interpretational processes including filtering, generalizations, abstract categorization and decision processes all contributing to the function of uncertainty reduction of the information processing system in the brain. The influence of such top-down modulatory processes may already be visible at very early levels of information processing. For example, at the level of the lateral geniculate nucleus neuronal activity is not only influenced by retinal input but also by figure-ground modulation (Jones et al., 2015). The most prominent theoretical description explaining the role of such top-down processes is certainly the predictive coding framework (Rao & Ballard, 1999; Friston, 2005). This framework encompasses a quite fundamental theory about how the brain works. It posits that perception – similar to Bayesian statistics – is a function of both sensory evidence and priors (Kersten et al., 2004). Although historically these ideas are quite old owing credit to von Helmholtz (1867) and cognitive scientists in the 1950ies and 60ies (e.g., Miller, Galanter, & Pribram, 1960; Norman, 1968; Neisser, 1967; Gregory, 1970), only currently the brain mechanisms implementing this top-down strategical mode of processing have

become accessible for scientific exploration. Moreover, these ideas have come to be related to the agenda of NCC research only recently (see Hohwy, 2013).

Taken together, the general idea of the predictive coding framework is that stimulus driven activity is insufficient. It does not by itself form a stable and cognitively veridical neural representation (see also Chapter 2 for the proposed importance of stability in conscious perception). Prior knowledge about the world can be used to facilitate and complement this process. Thus, it is also an important aspect in relation to the NCC. In particular, this stance should help us better understand the processes leading up to conscious perception. For example, it is possible that NCC will differ for stimuli that we have prior knowledge about and/or that we expect compared to stimuli that are unexpected or even completely new.

In any case, the effect of prior knowledge should be best observable with natural stimuli because the brain has the most prior knowledge about (or training with) this kind of information and neural networks should be optimally adapted to it (Kersten et al., 2004; see also **Rationale 2**). Millions of years have molded the brain under the environmental pressure featuring natural scenes and stimuli but simple artificial stimuli have a relatively short history and could not so dramatically have an impact on brain evolution. Note, however, that prior knowledge can manifest itself at many levels. It is quite impossible to present stimuli that do not relate to our knowledge about the world in any way. The most basic knowledge (e.g., typical statistics of the visual appearance of the environment, light from above, neighboring co-existence of light and shadow, texture invariants, etc.) is probably already built into the structure and the resulting processing algorithms of neural networks due to constant exposure (e.g. Berkes et al., 2011). Importantly, prior knowledge can also act on a faster time scale – perhaps through top-down modulations (e.g. Jones et al., 2015). The two following works are targeted at each of these levels.

## 5.1 Facilitation through familiarization

Previous studies have shown that prior knowledge about the upcoming stimuli can facilitate conscious perception (e.g. Aru et al., 2012a; Melloni et al, 2011; Mayer et al, in press). Yet it is not clear when after stimulus onset the effect of prior knowledge takes hold. If the above described theory of predictive coding holds true then prior knowledge may behave similarly to sensory evidence (see Melloni et al, 2011) and as a corollary, its effect on the processing of sensory evidence should take place already early in the processing hierarchy (Mayer et al, in press).

To study the effect of prior knowledge specifically on conscious visual perception and separate it from the pure effect of sensory evidence **Study IV** was conducted (see **Rationale 1**). We used a large set of photographs depicting people in natural settings (see **Rationale 2**). Random Gaussian noise was also added to the photographs to bring them close to the perceptual threshold. On every trial subjects had to indicate whether the person in the picture was male or

female (objective answer) and whether they perceived a person at all in the picture (subjective answer). Importantly, perception of the stimuli could be facilitated in two orthogonal ways. A stimulus could either contain less noise (i.e. more sensory evidence) or could have been seen in a previous familiarization phase (i.e. associated with prior knowledge). Both of these ways had an independent additive effect on the behavioral measures. While the subjects were solving the task their neural activity was measured via magnetoencephalography (MEG).

One way to investigate the neural markers of both facilitatory effects (increased sensory evidence and prior knowledge) is to conduct an analysis of variance for the effects of the corresponding factors on neural response strength. Note that this analysis is equivalent to contrastive analysis. The results of such an analysis indicated that the main effect of prior knowledge starts in the P300 range (from ca. 335 ms onward). The main effect of sensory evidence also covered the P300 range, but there was also an additional early effect (180–195 ms post stimulus). Similar to the behavioral results no interaction between the two factors was evident. From this pattern of results one could conclude that only sensory evidence has an earlier effect on neural response strength, but the effect of prior knowledge is post-perceptual. Thus, it would seem that contrary to the predictive coding framework prior knowledge does not contribute to perception directly at its earlier stage but through later memory related processes, for example (but see also Bachmann (2000) for a conciliation of the two stages).

However, the above described contrastive analysis need not link perception directly to the neural measures because the results of this contrast may also reflect other cognitive process in addition to the perceptual processes of interest (Aru et al., 2012b; see also Chapter 1.2). Thus, to investigate when prior knowledge exerts its positive influence on conscious perception a more sensitive analysis is needed to test our hypothesis. According to **Rationale 3** we again made use of the inter-individual variability in both neural and behavioral responses which should be related in meaningful and informative ways. The subject-specific difference in neural response strength between the conditions with and without prior knowledge was correlated with the same subject-specific difference but for the proportion of “seen” responses in both conditions (subjective answer). This correlation analysis indicated a strong negative relationship between the two measures at 80–95 ms after stimulus onset. This means that the bigger the gain in subjective perception was in the condition with prior knowledge the weaker neural responses tended to be in this early time window. The neural sources of this effect were localized to the early visual and parietal cortices. This effect was specific to subjective perception and prior knowledge – no similar correlation was found neither with changes in behavioral accuracy (objective answer) nor between changes in neural activity due to increased sensory evidence and the corresponding changes in subjective perception. Thus, the pattern of results hints at the possibility that objective performance may rely on different neural mechanisms compared to the subjective aspect of perception

(see also **Study 3**). Similarly, sensory evidence and prior knowledge may be coded in distinct ways (see also Aru et al., 2012a).

These results are among the first to demonstrate that priors can indeed have a very early and direct effect on conscious visual perception, but they also have important implications for the NCC. First of all, they demonstrate that NCC studies should not only take into account and equalize for sensory evidence, because previous interactions with stimuli (e.g. stimuli from previous trials) may also be reflected in the neural responses of interest (**Rationale 1**). Importantly, these two effects are probably distinctly different from each other. Sensory evidence can only affect the response evoked by it. Prior knowledge, however, will probably have to be reflected in the already ongoing activity of perceptual networks to have an early effect on evoked responses (Mayer et al, in press; see also **Rationale 4**).

Because the results do not indicate any changes in the typical NCC time range (starting from ca. 200 ms) the effect of prior knowledge can be said to be an NCC-pr. However, notice that it really seems to be a specific and direct effect on subjective perception. Thus, it may not be a more general early process, but only related to the mechanisms responsible for the specific contents of conscious perception. This again makes clear how important it is to understand the NCC-pr/NCC-co in addition to distilling the NCC proper (**Rationale 1**). Further work must clarify how this early effect changes subsequent information processing and possibly the NCC proper (see Melloni et al., 2011, for example).

## 5.2 Optimal stimuli for conscious perception

In **Study III** (and to some extent even in **Study IV**) we already examined the role of ongoing activity and how it can influence subsequent stimulus processing. However, in both studies ongoing activity was treated as “empty”, i.e. deprived of any specific stimulus content. Thus, these studies (as well as most of the other NCC studies) investigated the process of becoming conscious of some suddenly appearing visual content. In most natural situations, on the other hand, we remain conscious of our slowly changing environment for a while. It is reasonable to assume that the processes associated with maintaining a conscious perceptual state are at least to some extent different from the processes of creating the conscious percept anew. However, the former processes have been studied hardly at all (**Rationale 4**).

The process of maintaining a conscious perceptual state is particularly interesting in relation to the predictive coding framework. As already mentioned above, the most basic properties with predictive value are probably already coded into the connectivity patterns of the relevant neural networks. For example, Berkes et al. (2011) found that during maturation ongoing activity in V1 of ferrets becomes increasingly more similar to evoked activity, but only in relation to natural stimuli (i.e. movie scenes) and not artificial stimuli (e.g. drifting sinusoidal gratings). Thus, it seems that these neural networks have



developed to specifically accommodate a certain kind of input (the natural environment) and this is the reason why their default state becomes most similar to this particular evoked state. Consequently, it is possible that the visual cortex does not respond similarly or even equally well to all kinds of stimuli. Some stimuli may be more optimal and therefore may elicit a richer and/or more vigorous neural response state (see also **Rationale 2**). If, for example, the visual system is currently exposed to a natural movie scene its processing capacity (according to the predictive coding framework) will be much more engaged compared to looking at an empty static screen. This reasoning lead us to ask whether it is possible to detect those differences in the neural activity reflecting ongoing perception without any task demands in dealing with stimulation included in this perceptual environment.

We conducted **Study V** to test whether perturbing the visual cortex with TMS leads to different TMS-evoked brain responses depending on which kind of information the visual system currently holds and constantly updates. A no-report paradigm was employed. Participants solved a simple visual task in the center of the screen while the critical task-irrelevant background image was changed after each 30 second long trial. While the subjects were continuously looking at the screen we perturbed the brain (TMS targeted to V1) and recorded the resulting neural responses via electroencephalography (EEG). Importantly, the task-irrelevant backgrounds were either very simple stimuli (e.g., sinusoidal gratings with high or low spatial-frequency content, plain dark or light areas) or photographs of realistic environments displaying either nature scenes or man-made habitats.

An analysis of TMS-evoked EEG potentials showed that differences in mean amplitude of the potentials emerged as a result of the different contents of the task-irrelevant visual background constantly present in the fringe consciousness. Interestingly, the clearest differences in mean amplitude were evident between different subclasses of realistic photographs. Photographs of nature scenes elicited relatively more negative TMS-evoked responses compared to photographs depicting man-made habitats and these differences were already evident early in the N100 time range. Comparably clear differences were not present for any of the other comparisons between background classes or subcategories representing differences in the low level attributes of the visual background such as brightness or spatial frequency.

The results of **Study V** demonstrate that neural responses to brain perturbation by TMS depend on the concurrent state of the visual system, i.e. the information it currently holds (**Rationale 4**). The results also indicate that response dynamics are most discriminable for different subcategories of realistic stimuli (**Rationale 2**). It is thus possible that because the visual system is best adapted to the processing of realistic stimuli these kinds of stimuli also elicit a richer and/or more vigorous neural response state. It is in no way clear yet how the processes associated with ongoing perceptual states relate to the much more intensively studied evoked responses to transient stimuli. If the goal is to find the NCC, however, it may be worth considering if only concentrating

on the more easily controllable paradigms with transient stimuli may hinder our progress. For example, if similar paradigms to the one described above could be successfully used for decoding the contents of conscious perception this would make a strong case for the possibility that the markers of NCC may be more readily observable during ongoing perception when the involved neural networks have settled into a robust sustainable state. An interesting question would then also be whether such sustained NCC markers share a common process binding the particular contents to conscious perception or whether the NCC proper are unique for each percept (see **Study I** for general markers of conscious visual perception). These speculative ideas can only be answered by future research adhering to **Rationales 2** and **4**. Last but not least, our new method of perturbing the brain by TMS combined with ERP measurement dependent on the specifics of visual stimulation could be developed as an approach for decoding of mental contents by brain imaging.

## 6. States of consciousness

So far the discussion has concentrated exclusively on neural correlates associated with contents of conscious perception. **Studies I – IV** were aimed at investigating the process of becoming conscious of some content and the associated markers of NCC. **Study V** sought to broaden the field of NCC research by investigating and decoding the contents of ongoing conscious perceptual states. However, in the more common sense the expression “states of consciousness” is used for describing phenomena such as wakefulness, sleep, anesthesia or coma. Thus, states of consciousness do not distinguish between specific contents, but whether any contents are possible at all and to what extent.

Although the states and contents of consciousness have been studied in relatively isolated research efforts in the past, recently it has been acknowledged that both lines of evidence have to fit together in meaningful ways. Most importantly, an acceptable measure of consciousness should be able to distinguish both the states and the contents of consciousness (Schurger et al., 2015). Such a measure should make sure whether – and if yes, how – content-representing and state-controlling mechanisms interact in producing conscious experiences and the corresponding NCC (Bachmann, 1994; Hohwy, 2013; Bachmann & Hudetz, 2014; see also **Rationale 4**).

Sleep – and in particular non-rapid eye movement (NREM) sleep – constitutes a convenient state of unconsciousness for a comparison to wakefulness because it occurs naturally and thus does not require any invasive or artificial intervention. Although we probably are not completely unconscious during NREM sleep (e.g. Noreika et al., 2009; Siclari et al., 2013), a comparison to the fully awake state should nevertheless be good enough to bring out the differences between conscious and unconscious neural processes. For example, slow waves have been established as a rough indicator for the loss of con-



consciousness because they only occur during NREM sleep and not during wakefulness (Amzica & Steriade, 1995; Massimini et al., 2004). Importantly, it is possible to probe the state of consciousness with slow waves as a proximal indicator because slow waves can also be induced during sleep with TMS (Massimini et al., 2007).

Previous studies have not been able to successfully induce slow waves through occipital stimulation with a single strong TMS pulse (Massimini et al., 2007). This is perhaps because spontaneously occurring slow waves are not very prominent in visual and sensory areas (Murphy et al., 2009). Another reason could be that the early visual cortex requires a different kind of stimulation to induce the neural dynamics underlying slow waves. Emanating from our knowledge on visual masking (Bachmann, 1994, 2000; but see also **Study III**) we wanted to test (i) whether two neural responses elicited by two TMS pulses separated by 100 ms interact similarly to how two modal visual stimuli interact in masking and (ii) whether it is possible after all to induce slow wave responses if V1 is stimulated with two TMS pulses separated by this time interval (long-interval paired pulse stimulation). If effective, it would enable us to compare the differences between states of consciousness to the differences found in our previous typical contents of consciousness studies (**Studies I–IV**).

In **Study VI** subjects received single pulse and long-interval paired pulse stimulation while being awake as well as during NREM sleep. Neural responses were concurrently recorded via EEG. Results demonstrate several very interesting differences in TMS-evoked responses between the sleep and awake state, but also between the single and paired pulse regime specifically during sleep. Both stimulation regimes produced a stronger negative TMS-evoked response around 200–400 ms during NREM sleep. But only the second pulse in the paired pulse regime was also able to induce a prominent positive TMS-evoked response specifically in NREM sleep. This slow-wave-like EEG potential started around 200 ms after the second TMS pulse and lasted for over 500 ms. In contrast, the responses to the second pulse in the paired pulse regime during wakefulness did not exhibit any differences after 200 ms.

The results of **Study VI** indicate that it is indeed possible to induce slow brain potential waves reminiscent of sleep slow waves when early visual cortex is stimulated by long-interval paired TMS pulses (i.e. when similar timing parameters as with visual masking are used). One appealing explanation for this result is that the second TMS pulse was able to benefit from the effects of the first TMS pulse because it already brought the cortex into a favorable state. Thus, the long-interval paired pulse stimulation paradigm may prove to be an even more efficient way of inducing slow waves in sleep. Because slow waves are associated with several beneficial effects of sleep (see Discussion of **Study VI** for more details) this novel regime may also have therapeutic value for sleeping disorders and the accompanying cognitive impairments.

Although we neither propose to have developed a measure for the state of consciousness nor to have found a conclusive way to conciliate the neural markers of conscious state with the neural markers of conscious content a few

tentative remarks with regard to the previously discussed markers of NCC are nevertheless possible. First of all, we were able to replicate the findings showing that slow waves are a sign of the unconscious state. Thus, the strong positive response to the second TMS pulse can be regarded as a neural marker of unconsciousness. Interestingly, this marker starts to arise around 200 ms post-stimulus (i.e. the second pulse) which is about the time that content-based NCC markers are estimated to onset in the awake state (see **Study I–III**). The first TMS pulses generated a negative EEG potential specifically during sleep which also started around 200 ms post-stimulus. Again, one might interpret it tentatively as a neural marker of unconsciousness. This sleep-specific negative component should not be confused with the visually evoked N200, however, because it lacks the topographic specificity on occipito-temporal regions. Therefore, the N200 remains a marker of the sensory aspect of consciousness – possibly indexing the general process of becoming conscious of any stimulus (see **Study I** for general markers of conscious visual perception). Similarly, slow negativity which seems to indicate increased arousal state (Murd et al., 2010) and has been associated with consciousness (He & Raichle, 2009) may constitute a good indicator of wakefulness thus supplementing the above described slow positivity during sleep. On the other hand, the absence of a clear brain potential in response to the second TMS pulse in the long-interval paired pulse protocol could become a marker of (perhaps unreported) consciousness in patients with communicative handicaps. This possibility of instrumental diagnostics of consciousness of course has to be supported in future studies using anesthetized subjects contrasted to un-anesthetized, conscious subjects.

## CONCLUSIONS

The goal of the present work was to study the neural basis of conscious experience in general and the neural correlates of consciousness (NCC) in particular. To that end, NCC were operationalized as EEG markers of conscious visual perception obtained in the experiments using contrastive analyses. Although consciousness is an exceedingly difficult phenomenon to study or even grasp conceptually we nevertheless believe that by proceeding with the research step-by-step one can get closer to the truth of it. The present work has tried to contribute to this research effort by following 4 general rationales:

1) More refined experimental paradigms are needed to control for or investigate possible NCC-pr/NCC-co.

**Study I** was designed to control for stimulus type specific NCC-pr/NCC-co. The goal was to find out which markers of NCC are general across stimuli and reliable enough within one study despite the pitfalls of the contrastive method. N200 and P300 were the two ERP components that satisfied these criteria. Nevertheless, both of these components may have also represented general NCC-pr/NCC-co that almost always may accompany the NCC proper. Thus, **Study II** was carefully designed and conducted to specifically investigate whether P300 may actually index a NCC-co reflecting working memory processes independent of consciousness. However, results again identified both N200 and also P300 as the markers of NCC. **Study III** used a novel pre-stimulus masking paradigm with TMS to investigate whether more global network effects could constitute a critical, yet previously unexplored NCC-pr. Results did support the hypothesized importance of network connectivity for conscious perception and also the role of N200 as a marker of NCC. But they also exemplified that identifying markers of NCC is not the same as identifying the actual NCC themselves. After all, N200 may have indexed many other parallel processes besides the processes constituting NCC or all 3 types of NCC may have overlapped during that time. It is impossible to conclude which processes were affected exactly. Finally, **Study IV** sought to investigate the specific role of prior knowledge for NCC-pr by concurrently controlling for the well-known effect of sensory evidence. Results indeed demonstrated a very early effect that was only specific to prior knowledge (not sensory evidence) and conscious visual perception (not objective task performance). Thus, **Study IV** demonstrated that NCC-pr may not just be any processes preceding NCC proper in time, but may well be *directly* and *specifically* related to conscious perception.

2) The stimuli used in typical paradigms are too restrictive and artificial. This may distort or bias the results and pose an obstacle for revealing the general markers of consciousness invariant to the narrow range of stimulus contents.

If a study employs a restrictive stimulus set then perceptual events become inevitably more predictable. **Study IV** indeed demonstrated that prior know-

ledge about upcoming stimuli has a direct influence on conscious perception and is associated with an early neural effect. **Study V** showed that at least some stimuli can be distinguished on the basis of neural responses to TMS perturbation during prolonged perception. This indicates that the neural responses and thus also the NCC may possibly be different to some extent for different types of stimuli. Note also that the critical results of both **Study IV** and **Study V** were obtained with realistic complex stimuli which are hypothesized to be ideally suited for the visual system. Up to now too many of the NCC studies have used very simple stimuli, which may hinder the quest for NCC. Finally, in **Study I** we avoided this confound of predictability and lack of general status of markers due to stimulus specificity, both associated with restricted content. This was achieved by presenting a heterogeneous stimulus set including many complex stimuli such as faces, animals or man-made objects.

3) More attention should be given to the variability in results and how it can be explained.

Variability of results comes in many forms (behavioral as well as neural) and has been a constant concern in cognitive research from its very beginnings. Oftentimes it is regarded as an annoying (or possibly even dangerous) source of noise and should thus be ignored or eliminated, if possible. However, variability can also be exploited to conduct more sensitive tests and obtain more meaningful results. In **Study I** we purposefully introduced variability to the stimulus material in order to make perceptual events less predictable and thus overcome a known confound in NCC research. In the same study we also tried to estimate the variability of NCC markers within one single paradigm. As it turned out, the markers of NCC – their occurrence but even more so their onset latency – can vary considerably if a contrastive analysis is used. In an effort to explain the source of this extensive variability in NCC marker onset latencies we analyzed relevant single trial parameters and found out that variability in NCC marker onset latencies is best explained by amplitude fluctuations in the condition *without* conscious perception. Therefore, it is possible that stability of evoked responses is a hallmark of conscious perception. In **Studies III** and **IV** we used the relationship between inter-subject variability in behavioral effects and neural responses to conduct more sensitive tests for our research questions. In **Study III** this enabled us to find for the first time a neural marker for pre-stimulus masking with TMS. In **Study IV** it led to the identification of an early neural marker for the specific effect of prior knowledge on conscious visual perception. Thus, in both of these studies we tried to overcome the problematic contrastive approach by employing an alternative analysis method.

4) The ongoing state of the brain must be taken into account when investigating the neural markers of consciousness as a response to natural and artificial perturbations of the brain.

It goes without saying that perception and behavior are not solely based on the activity of isolated brain areas performing specific tasks. These areas also

form intricate networks and only the concentrated ongoing effort of these networks is able to maintain our stable perception of the world around us. It is unlikely that we will understand the NCC without first understanding the effects of such relevant network activity. For example, **Study III** was designed to investigate whether pre-stimulus TMS masking is also possible through stimulation of not the early visual cortex but instead a distant frontal area of the brain. If yes, it would support the assumption that the ongoing state of a larger task-related network is critical for perception. And indeed, results demonstrated a clear masking effect with frontal TMS. **Study V** approached the process of conscious perception in a more unconventional way. The goal was to find out whether neural responses to TMS perturbation differ depending on which kind of information the visual system holds during prolonged conscious perception. As the results were confirmatory at least for some types of stimuli it may be well worth studying in the future whether the markers of NCC are more easily identifiable for ongoing perceptual states. It will also be important to understand how the process of ongoing perception relates to the much more studied process of transient perception. Finally, **Study VI** investigated the neural markers of sleep versus wakefulness (i.e. different states of consciousness not contents of consciousness). Results demonstrate that it is possible to induce slow waves (a well-known marker for the loss of consciousness during sleep) also from the early visual cortex if a long-interval paired pulse TMS regime is employed. Specifically the second pulse produced a response indicative of the state of (un)consciousness. Interestingly, this massive positive response started around the same time (ca. 200 ms post-stimulus) as the markers for conscious visual perception are estimated to arise (see **Study I**). Thus, the results indicate that the markers for states of consciousness may be related to the markers for contents of consciousness in meaningful and informative ways.

Not surprisingly, the presently discussed work in accordance with the 4 rationales has not conclusively solved all the problems facing consciousness research today. The phenomenon of consciousness is just too complex and challenging to be completely understood in the near future by anyone. My hope is simply that these studies will be as useful to our fellow researchers as they have been for us in furthering our understanding of the topic and its critical points. Thus, without further reservations, we remain most curiously expectant of all new advancements toward a better understanding of the neural correlates of consciousness and their markers.

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## SUMMARY IN ESTONIAN

### **Teadvuse neuronaalsete korrelaatide uurimismetoodika edasiarendusi**

Tänapäeval on üldiselt aktsepteeritud, et teadvuse neuronaalsete alustalade mõistmiseks on esimese sammuna tarvis täpsemalt määratleda ja tundma õppida teadvuse neuronalseid korrelaate – neid ajuprotsesse, mis on minimaalselt tarvilikud mingi kindla teadvuselamuse jaoks (Koch, 2004). Kuna nägemismeele on meie jaoks kõige tähtsam tajumodaalsus, mida on põhjalikult uuritud nii eksperimentaalpsühholoogide kui ka neurobioloogide poolt, on valdav enamus senistest käesoleva uurimisvaldkonna teadustöödest keskendunud visuaalsete teadvuselamuste neuronaalsetele korrelaatidele. Ka käesolev töö on just nimelt suunatud visuaalse teadvustamisega seonduvate protsesside ning nende ajukuva abil registreeritavate markerite uurimisele.

Hoolimata sellest, et vastavat uurimistööd on tehtud palju, on tulemused olnud väga erinevad. Vahel leitakse, et millegi teadvustamine on pigem hiline protsess, mis seondub frontoparietaalse võrgustiku aktiivsusega (nt Sergeant jt., 2005; Del Cul jt., 2007), kuid teiste uuringute andmetel on teadvuse korrelaadid pigem varajased ja ilmnevad sensoorsetes piirkondades (nt Pins & Ffytche, 2003). Viimasel ajal toonitatakse eelkõige nende kahe äärmuse – 100 ja 300 millisekundi – vahel oleva latentsiajaga korrelaatide olulisust (Koivisto & Revonsuo, 2010). Üks põhjus, miks erinevate tööde tulemused nii vastandlikud võivad olla, on seotud probleemidega kontrastiivanalüüsi kasutamisel. Kontrastiivanalüüs on teadvuse korrelaatide tuvastamise enim levinud meetod. Selle käigus võrreldakse teadvustamise taganud katsekordadel mõõdetud ajutegevust teadvustamist mitte taganud katsekordade ajutegevusega lootuses erinevusena leida markerid just nimelt nendele protsessidele, mis otseselt seonduvad teadvuselamusega. Samas ei pruugi aga teadvustamise protsessid olla ilmtingimata ainukeseks erinevuseks nende kahe tingimuse vahel. Erinevusena võivad välja tulla ka protsessid, mis süstemaatiliselt eelnevad teadvuse korrelaatideks olevatele protsessidele või neile järgnevad, kuid sealjuures ise otseselt teadvustamise protsessid ei ole (Overgaard, 2004; Bachmann, 2009; Aru et al., 2012b; de Graaf et al., 2012).

Kuigi kontrastiivanalüüsiga kaasnev metodoloogiline probleem on nüüdseks juba mitu aastat teada, pole sellele veel veenvat lahendust leitud (Aru et al., 2015). Et sellegipoolest liikuda teadvuse korrelaatide ning nende markerite parema mõistmise suunas, on tarvis jätkata kontrastiivanalüüsi alternatiivide otsinguid kui ka üritada kontrastiivanalüüsiga kaasnevaid ohte vältida. Need eesmärgid on käesolevas töös täide viidud nelja üldist põhimõtet järgides:

1) Teadvuse korrelaatide tuvastamiseks on tarvis kasutada senisest rafineeritumaid katseparadigmasid, vältimaks või uurimaks teadvusega süstemaatiliselt kaasnevaid teisi protsesse.

**Uurimus I** eesmärgiks oli vältida erinevate stiimulitüüpidega kaasnevaid kitsalt spetsiifilisi protsesse ja leida sellised visuaalse teadvustamise markerid, mis on üldomased erinevatele stiimulitele ning on hoolimata kontrastiivanalüüsi probleemist usaldusväärsed ühe katseparadigma siseselt. Elektroentsefalograafia (EEG) sündmuspotentsiaalide komponendid N200 ja P300 vastasid nimetatud tingimustele. Siiski on aga võimalik, et üks nendest markeritest või isegi mõlemad on hoopis seotud teadvustamisele eelnevate või sellele järgnevate üldiste protsessidega, mis hoolimata stiimulitüübist alati teadvusega kaasnevad, olemata iseenesest teadvustamisprotsessid. **Uurimus II** üritas seega hoolikalt planeeritud ning läbiviidud katseparadigma kaudu testida, kas P300 võib hoopiski tähistada teadvustamisele järgnevaid töömälu protsesse. Tulemused näitasid aga taas, et nii N200 kui ka P300 on mõlemad visuaalse teadvustamise markerid.

**Uurimuses III** rakendati uudset stiimulieelse transkraniaalse magnetstimulatsiooniga (TMS-iga) maskeerimise paradigmat eesmärgiga selgitada, kas globaalsete neurovõrgustike käimasolev seisund, mida moduleeritakse teadvustamise objektiks oleva stimuli suhtes mittespetsiifiliselt kujutab endast olulist teadvustamisele eelnevat protsessi. Tulemused tõepoolest toetasid seda oletust ning taaskord kinnitasid N200 komponendi olulisust visuaalse teadvustamise markerina.

**Uurimus IV** eesmärgiks oli määratleda stiimulikohaste eelteadmiste spetsiifiline roll teadvustamise protsessi käigus, kontrollides samas stiimulite objektiivse nähtavuse teadaolevat kaasmuutuvat mõju. Tulemused näitasid, et sellised eelteadmised on seotud väga varajase neuronalse efektiga ning see efekt on spetsiifiline just nimelt teadvustatud taju jaoks.

2) Eelnevates töödes on tihti kasutatud liiga piiratud ulatusega ning kunstlikke stiimuleid. See võib tulemusi kallutada ning takistada stiimulite sisust sõltumatute üldiste teadvuse korrelaatide tuvastamist.

Kui katses kasutatakse ainult vähest hulka erinevaid stiimuleid, siis muutuvad need stiimulid suurel määral ettearvatavaks. **Uurimus IV** tulemused kinnitasid, et eelteadmised stiimulite kohta mõjutavad otseselt nende stiimulite teadvustamist ning omavad väga varajast neuronaalset efekti. **Uurimus V** tulemused näitasid, et vähemalt osasid loomulikku keskkonda iseloomustavaid stiimuleid pidevalt vaadates on võimalik neid stiimuleid eristada TMS perturbatsioonidega kaasnevate neuronaalsete vastuste põhjal. Seega võib oletada, et ka teadvuse neurokorrelaadid võivad teatud määral varieeruda erinevate stiimulite lõikes. Siinkohal on tähtis lisada, et nii **Uurimus IV** kui ka **Uurimus V** kriitilised tulemused ilmneseid komplekssete realistike stiimulite korral. Arvatavasti on sellised stiimulid visuaalse süsteemi jaoks optimaalsed võrreldes lihtsate kunstlike stiimulitega (Kersten jt., 2004). Lähtuvalt eelmainitud põhimõtetest ja kooskõlas teiste meie tulemustega vältiti **Uurimus I** raames piiratud ulatusega ning kunstlike stiimulitega kaasnevate kaasmuutuvate ning ülemäära spetsiifiliste faktorite ebasoovitavaid mõjusid. Selleks esitati katseisikutele

suurel hulgal erinevaid stiimuleid, mis hõlmasid ka komplekssemaid figuure nagu näiteks näod, loomad ning tööriistad.

3) Rohkem tähelepanu tuleks pöörata tulemuste variatiivsusele ning küsimusele sellest, kuidas seda variatiivsust seletada.

Kõikide katsete tulemused varieeruvad nii käitumuslikul kui ka neuropaalsel tasemel. Seda variatiivsust saab ära kasutada, et läbi viia tundlikumaid teste ning seekaudu saada tähendusrikkamaid tulemusi.

**Uurimuses I** kasutati meelega ulatuslikult varieeruvaid stiimuleid, et muuta neid vähem etteaimatavaks ja vähem kitsalt-spetsiifiliseks. Samas uuringus seati eesmärgiks ka hinnata, kui variatiivsed võivad teadvuse neurokorrelaatide markerid olla ühe katse siseselt. Tulemused näitasid, et markerid – nii nende esinemine, aga eelkõige nende algusaeg – olid märkimisväärselt variatiivsed. Seda variatiivsust seletas kõige paremini EEG potentsiaalide amplituudi kõikumine tingimustes, kus sihtstiimulit ei teadvustatud. Seega võib oletada, et teadvustamise iseloomulik tunnus on neuropaalse aktiivsuse stabiilsus vastusena stimulatsioonile.

**Uurimustes III ja IV** võeti vaatluse alla seosed käitumusliku ning neuropaalse variatiivsuse vahel, et tundlikumalt käsitleda töö keskseid uurimusküsimusi. **Uurimuses III** võimaldas selline lähenemine leida seni mitteteadaolevad ja üldistatud andmetes peitu jäävad teadvuse neuropaalsed korrelaadid stiimulielse TMS-iga maskeerimise paradigmas. **Uurimuses IV** lubas see lähenemine tuvastada eelteadmise seostuva varajase neuropaalse efekti teadvustamisele. Seega leiti mõlemas uuringus hea alternatiiv problemaatilisele traditsioonilisele kontrastiivanalüüsile.

4) Kui uuritakse teadvuse korrelaatide markereid seoses loomulike ning kunstlike aju perturbatsioonidega peab arvesse võtma aju käimasolevat seisundit.

Ilmselt ei põhine tajut ja käitumine ainult üksikute isoleeritud ajukeskuste aktiivsusel. Need keskused moodustavad keerulisi võrgustikke ja ainult nende võrgustike pidevalt jätkuv koostöö tagab stabiilse tajut meid ümbritsevast maailmast. Tõenäoliselt ei suuda me mõista teadvuse korrelaate enne kui hakkame mõistma globaalsete võrgustike aktiivsuse efekte. Seondult sellega näitasid **Uurimus III** tulemused, et teadvustamise stiimulielne TMS-iga maskeerimine pole mitte ainult võimalik esmase visuaalse korteksi stimulimise kaudu, vaid ilmneb ka siis, kui TMS on suunatud aju frontaalsetele aladele. Seega viitavad tulemused tõsiasjale, et teadvustamise jaoks on oluline ka globaalsema võrgustiku parajasti käimasolev seisund.

**Uurimus V** lähenes visuaalsete teadvuselamuste uurimisele ebatüüpilise nurga alt. Eesmärk oli uurida, kas neuropaalne vastukaja TMS perturbatsioonile erineb olenevalt sellest, millist informatsiooni visuaalne süsteem parasjagu töötles hoiab. Kuna tulemused näitasid, et käimasoleva kestvalt kogetava tajut sisud on tõepoolest teatud juhtudel TMS perturbatsiooni abil EEG sündmuspotsentiaalide (ERP) markerites eristatavad, tasub tulevikus täpsemalt uurida, kas teadvuse korrelaadid võiksid olla hõlpsamini tuvastatavad pidevalt kestvate

tajusisude jaoks. Lisaks tuleks selgitada, kuidas pidevalt kestvate tajude neuro-naalsed korrelaadid suhestuvad transientsete stiimulite teadvustamise korre-laatidega.

**Uurimus VI** keskendus unenägudevaba unega kaasnevate ja virgeolekuga kaasnevate ajuprotsesside neuronaalsete markerite võrdlevale uurimisele (uuriti teadvusseisundeid, mitte teadvuse sisu). Tulemused näitasid, et aeglaseid ERP laineid, mis on uneajale iseloomuliku teadvusetuse hästi tuntud markerid, on võimalik TMS-i abil esile kutsuda ka esmase visuaalse korteksi stimuleerimi-sega juhul kui kasutada kahte TMS impulssi, mis esitatakse 100 ms pikkuse ajavahega. Huvitaval kombel algas aeglasi laineid tähistav tugev positiivne EEG potentsiaal umbes samal ajal (200 ms pärast viimast TMS impulssi) kui tavaliselt ilmuvad visuaalse teadvustamise markerid (vaata nt **Uurimus I**). Seega viitavad tulemused sellele, et teadvusseisundite markerid ja teadvuse sisu markerid ei pruugi olla eraldiseisvad nähtused, vaid näikse olevat omavahel seotud tähendusrikkal moel. Oluline **Uurimuse VI** tulemus näitas, et teadvusel virgeolekus inimese aju ei vasta teisele TMS impulsile märkimisväärsel määral samas kui uneseisundis kutsub teine impulss esile suureamplituudsed aeglased lained. Selles tulemuses peitub potentsiaal teadvusseisundi diagnostika meeto-dite väljaarendamiseks neuroloogiakliinikus.





## **PUBLICATIONS**

## CURRICULUM VITAE

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Since 2011 Scientific lab technician at the Cognitive psychology lab, University of Tartu (<http://www.bachmannlab.com/>)  
2009–2010 Student research assistant at the Department of Psychology, University of Potsdam, Germany  
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### Publications:

Aru, J., Rutiku, R., Wibral, M., Singer, W., & Melloni, L. (2015). *Early effects of previous experience on conscious perception*. Manuscript submitted for publication.  
Aru, J., Stamm, M., Rutiku, R., & Bachmann, T. (2015). TMS to occipital cortex in the awake state and NREM sleep. Toward a Science of Consciousness 2015, Proceedings of the 21<sup>st</sup> annual international conference (p. 120), Helsinki: Hakapaino OY.  
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- Stamm, M., Aru, J., Rutiku, R., & Bachmann, T. (2015). Long-interval paired pulse TMS leads to late positive wave components in NREM sleep. *Brain Stimulation*, 8 (Abstracts, 263), 392.

## ELULOOKIRJELDUS

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### Uurimistöö põhisuunad:

teadvus; nägemistaju; elektrofüsioloogia

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