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# The Enhancement of Sensory Perception through Non-Invasive Brain Stimulation

A thesis submitted to attain the degree of

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Presented by

**Onno Leendert Bernardus van der Groen**
MSc in Cognitive Neuropsychology – VU University Amsterdam
Born on 17.11.1988
Citizen of the Netherlands

accepted on the recommendation of

*Prof. Dr. Nicole Wenderoth*
*Prof. Dr. Daniel Kiper*
*Dr. Arko Ghosh*

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# Acknowledgements

Undertaking this PhD has been a marvellous ride with highs and lows. Sometimes ideas work out, data is significant and new ideas emerge. Sometimes ideas don't work out, the data is not significant, you have to change your experiment all over again, papers get rejected and you are wondering if it is worth pushing through. During these highs and lows I knew there were always people around I could rely on to celebrate with or to turn to for help and support. It is these people I would like to thank because without you this thesis wouldn't exist.

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# Abstract

The human brain has a fascinating ability to perceive and process information from the world around us. It is the basis for the way in which we experience our environment, and therefore how we interact with it. The perception and processing of the information is not free of noise. Whilst it makes sense to think that less background noise in a perceptual signal makes it easier to perceive, it is in fact not that simple. A phenomenon known as Stochastic Resonance (SR), where an optimal level of noise can be added to actually enhance the strength of a signal, has been demonstrated in many natural systems. The research into SR in human perception to date has largely been restricted to studies involving the peripheral nervous system. However, a critical question with significant clinical and theoretical implications remains to be answered: How does noise influence central mechanisms of sensory information processing in humans? This question is the overarching motivation for the experiments presented in this thesis, which uses transcranial Random Noise Stimulation (tRNS) to add noise to the central nervous system. We investigate how this method of non-invasive brain stimulation influences sensory perception in humans using behavioural and computational modelling approaches.

In the first study outlined in this thesis we present ground-breaking work to demonstrate that applying noise to the brain directly with tRNS can enhance the detection performance of weak visual stimuli. The mechanism of this effect can be explained by SR principles. In the second study, we go a step further and demonstrate that this effect is not limited to simple contrast detection, but that tRNS can also enhance performance on a perceptual decision-making task. Computational modelling in this study shows that tRNS can improve the quality of the stimulus representation in the brain on which the decision is based. These results suggest that tRNS is able to enhance human perception by modulating the signal to noise ratio (SNR). In the third study, we demonstrate that tRNS can also influence bistable-perception, however, only when specific conditions are met, a result which also highlights the limitations of tRNS.

This research is the gateway to a better understanding of the role of different noise levels within the brain in both healthy and clinical populations. There is significant commercial interest in the development of devices that improve cognitive and sensory perceptual function in the general population, in specialized professions, as well as

clinically with the suggestion that disorders such as autism and schizophrenia may involve excessive or insufficient levels of noise within the brain. Therefore, our findings are not only of interest to the scientific community, but also for a range of applications in commercial and medical industries.

# Zusammenfassung

Das menschliche Gehirn hat die faszinierende Fähigkeit, Informationen aus der Welt um uns herum wahrzunehmen und zu verarbeiten. Es ist die Basis für die Art und Weise, in der wir unsere Umwelt erleben und mit ihr interagieren. Die Prozessierung und Verarbeitung ist dabei nicht frei von Hintergrundrauschen. Während es auf den ersten Blick sinnvoll erscheinen mag, dass weniger Hintergrundrauschen es einfacher macht ein Signal zu erkennen, ist es in Wahrheit nicht so einfach. Stochastische Resonanz (SR) ist ein physikalisches Phänomenon, in welchem optimales Rauschen die tatsächliche Stärke eines Signals erhöhen kann. Dies wurde bereits in vielen natürlichen Systemen gezeigt. Bisherige Studien zur Erforschung der SR in der menschlichen Wahrnehmung beschränkten sich jedoch weitgehend auf das periphere Nervensystem. Allerdings bleibt eine kritische Frage mit erheblichen klinischen und fundamentalen Implikationen weiterhin zu beantworten: Wie beeinflusst Hintergrundrauschen die zentralen Mechanismen der sensorischen Informationsverarbeitung beim Menschen? Diese faszinierende Frage ist die zentrale Motivation für das vorliegende Forschungsprojekt. In dieser Arbeit verwenden wir transkranielle Rauschstimulation (`transcranial random noise stimulation`, tRNS), um dem Zentralnervensystem künstliches Hintergrundrauschen hinzuzufügen. Wir untersuchen, wie diese Methode der nicht-invasiven Hirnstimulation die sensorische Wahrnehmung beim Menschen beeinflusst.

Im ersten Projekt dieser Arbeit präsentieren wir bahnbrechende Arbeiten, um zu zeigen, dass die Hinzugabe von optimalem Hintergrundrauschen im Gehirn mittels tRNS das Erkennen von schwachen visuellen Reizen verbessern kann. Der Mechanismus dieses Effektes lässt sich durch SR-Prinzipien erklären. Im zweiten Projekt gehen wir noch einen Schritt weiter und zeigen, dass dieser Effekt nicht auf einfache Kontrastwahrnehmung beschränkt ist, sondern dass tRNS auch die Leistung während einer perzeptuellen Entscheidungsfindungsaufgabe verbessern kann. Computermodelle, welche auf dieser Studie basieren, zeigen dass tRNS die Stimulusräpräsentation im Gehirn verbessern kann. Diese Ergebnisse deuten darauf hin, dass tRNS in der Lage ist, die menschliche Wahrnehmung durch Modulation des Signal-Rausch-Verhältnisses (SRV) zu verbessern. Im dritten Projekt zeigen wir, dass tRNS zusätzlich auch die bistabile Wahrnehmung beeinflussen kann, jedoch nur, wenn

bestimmte Bedingungen erfüllt sind. Dieses Ergebnis zeigt auch die möglichen Grenzen von tRNS auf.

Die vorliegende Arbeit legt das Fundament zum besseren Verständnis des Einflusses von Hintergrundrauschen auf das Gehirn in gesunden und klinischen Populationen. Es besteht ein erhebliches kommerzielles Interesse an der Entwicklung von Geräten in der Medizintechnik, welche die kognitive und sensorische Wahrnehmungsfunktion in der Allgemeinbevölkerung, in Fachberufen sowie auch in klinischen Populationen verbessern. Beispielsweise können Krankheiten, wie Autismus und Schizophrenie, auf übermässiges oder vermindertes Hintergrundrauschen im Gehirn zurückgeführt werden. Daher sind die vorliegenden Ergebnisse nicht nur in wissenschaftlicher Hinsicht interessant, sondern auch für die Anwendung zu kommerziellen und medizinischen Zwecken.

# Chapter 1: Introduction

Noise is typically detrimental for the processing and transfer of signals. There are many examples where noise is reduced to a minimum in order to enhance the signal-to-noise ratio (SNR). For example, neuroscientists recording brain activity with an electroencephalogram (EEG) will often collect their data in a Faraday cage which functions to block electromagnetic interference in order to enhance the SNR of the very weak brain signals that are being recorded. In this thesis noise is defined as random or unpredictable fluctuations and disturbances that are not part of a signal. In sensory information processing, noise can have different origins (Faisal, Selen, & Wolpert, 2008). For example, it can occur in the signal in the outside world, which we classify as external noise. Noise can also occur in the nervous system, which we will classify as biological noise. In some instances, small amounts of noise can be beneficial for the output of some systems, a phenomenon known as Stochastic Resonance (SR). Other constructive effects of noise have been described elsewhere (see (Rajasekar & Sanjuan)). SR occurs when noise added to a non-linear system can enhance some aspect (e.g. SNR or signal amplitude) of the system output. The concept of SR was first introduced at the 1980 NATO International School of Climatology to describe a possible explanation for the relatively periodic recurrence of the Earth's Ice Ages every 100,000 years (Benzi, Sutera, & Vulpiani, 1981). Since then, it has been extended across research in the fields of medicine, psychology, biology, environmental science, engineering and robotics.

## 1.1 Types of Stochastic Resonance

### *1.2.1 Dynamical-SR*

Originally it was thought that SR was limited to dynamical bistable systems (M. D. McDonnell, Stocks, Pearce, & Abbott, 2008) as depicted in Figure 1-1. The two troughs indicate the two stable states and the orange ball indicates the current state of the system. The two stable states are separated by a threshold/barrier that needs to be overcome in order to switch from one stable state to the other. A weak oscillatory signal changes the energy landscape (i.e. the gradient between peaks and troughs), however on its own, the signal is not able to cause a shift in the state of the system. It requires the addition of an optimal level of noise to induce a shift. In its original application to climate shifts, the two stable states were an ice-age and a green age. The noise in this original model were daily and seasonal variations in the climate (Benzi et al., 1981). Subsequent research proved this was an inadequate explanation for climate shifts, however, this concept has since been successfully applied in other domains.

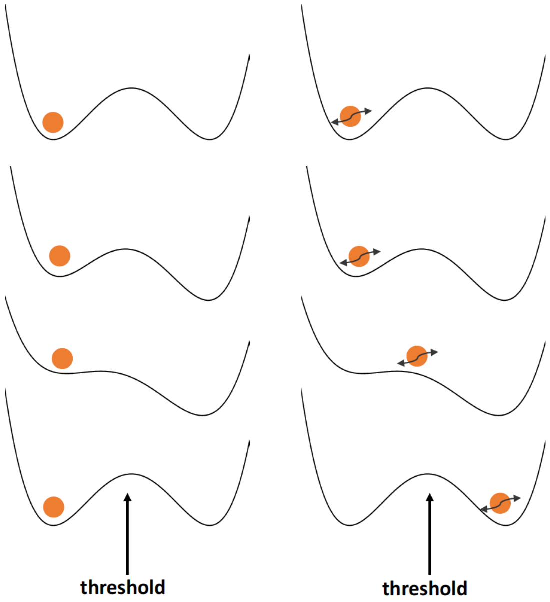

*Figure 1-1* Dynamical stochastic resonance in a bistable system.
The current state is represented by the orange circle (represented on the left). The energy landscape consists of two stable states (represented by troughs) separated by a threshold/barrier which varies with a weak oscillatory signal. A transition from one state to another is only possible with the addition of an optimal level of noise (represented on the right) to overcome the threshold. The optimal level of noise can be mathematically determined. For the optimal noise level the Kramer's rate must match half the period of the external driving force (Anishchenko, Neiman, Moss, & Shimansky-Geier, 1999). Kramer's rate is a physics concept defined as the escape rate from a stable state in the absence of a signal (Bulsara & Gammaitoni, 1996).

There are several methods to quantify the SR-effect in dynamical systems. One measurement is the residence time, which is the time the system spends in one of the states before switching to the other state (Longtin, Bulsara, & Moss, 1991; Rajasekar & Sanjuan; Wiesenfeld & Moss, 1995). The driving signal (sine-wave) changes the energy landscape (Figure 1-2 A) at the frequency of the signal. When no noise is present, the residence time is infinite because the system will stay in its initial state, because noise must be present to induce a switch. When the noise level increases, the system may transition to the other state. When the noise is further increased to the optimal noise level, then the system will begin switching periodically. Further increasing the noise results in a decrease in the periodicity. In addition, the switching rate can also be calculated. This is the number of switches between the states in a predefined time range. This increases linearly with increasing noise intensity. In Figure 1.2A it is clear that when an optimal level of noise is applied, variation in residence time ($T_{mr}$) is very small. The switching rate does not contain any information about the periodicity of the switching. Therefore, to fully capture the dynamics of noise induced SR in a bistable system, both the residence time and switching rate need to be taken into consideration (Rajasekar & Sanjuan).

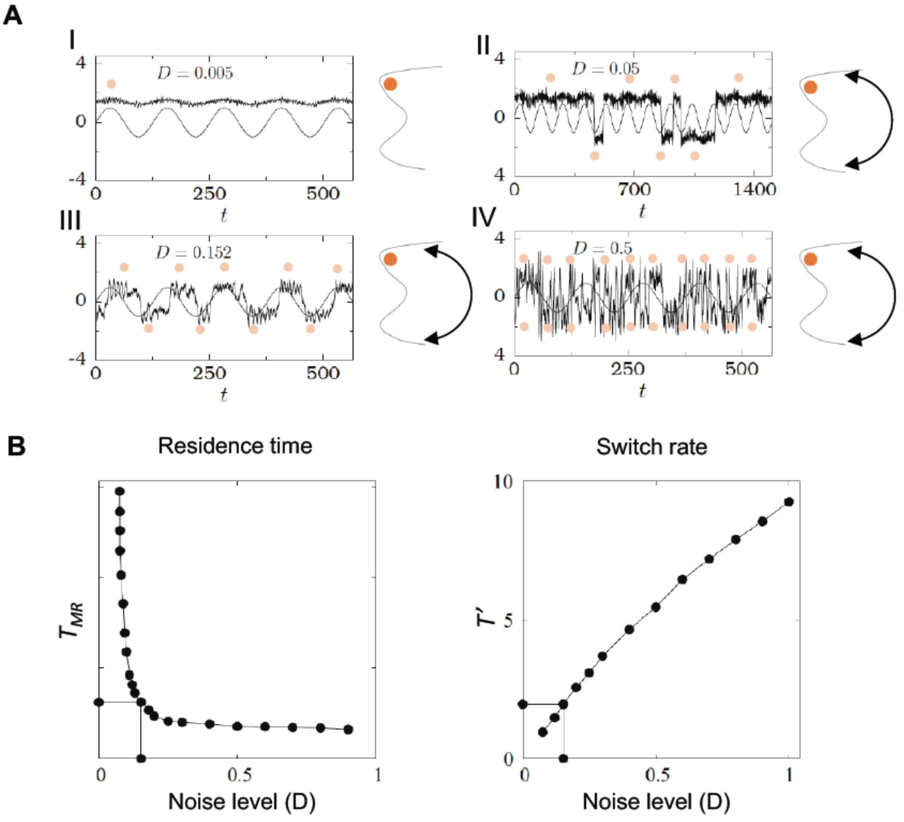

*Figure 1-2 Outcome measurement of the dynamical-SR-effect.*
**A)** A driving signal (sine-wave) changes the energy landscape (depicted on the right) at the frequency of the signal. When a small amount of noise (D, arbitrary unit) is added, the system stays in its original state despite the driving signal (I). When the noise level increases, the system begins sporadically switching between states (II). With an optimal level of noise the system will switch between states at regular intervals, (III), and with too much noise the switching becomes erratic (IV). **B)** Two common outcome measures of SR in dynamical systems. The points on the x- and y-axis represent the optimal noise level. In the image on the left, the residence time ($T_{mr}$) decreases with increasing noise levels. In the image one the right the switch rate (T') increases with increasing noise levels. Image adapted from (Rajasekar & Sanjuan).

So far we have limited the discussion of the SR-effect to bistable systems. These systems naturally stay in one of two possible stable states. However, SR can also occur in excitable systems with only one stable state, which is known as non-dynamical or threshold SR (K. Wiesenfeld, D. Pierson, E. Pantazelou, C. Dames, & F. Moss, 1994).

### *1.2.2 Non-dynamical SR*

In 1994, Wiesenfeld and colleagues published an influential paper in which they demonstrated for the first time that the SR-phenomenon can also be applied to excitable threshold systems with only one stable state, in this case, in sensory neurons in crayfish (K. Wiesenfeld et al., 1994). A characteristic of non-dynamical systems is that after crossing the threshold, the system consistently returns to its rest state after a defined refractory period. In order for non-dynamical SR to occur, the signal must be subthreshold in order to not produce an output in the system. A suprathreshold signal is already detected without noise, therefore a SR-effect does not occur. The probability of threshold crossings increases when an optimal level of noise is added to the subthreshold signal. The system will produce an output when the signal plus optimal noise level crosses the threshold. With too much noise the signal gets buried and the signal is no longer distinguishable from the noise. In this case threshold crossings occur at random and do not provide any information about the underlying signal.

The residence time and switch rate are not useful outcome measurements in the case of non-dynamical SR. Instead, the SNR is typically calculated to quantify the SR-effect. Below is a generic formula that quantifies the SNR. The formula is generic because it can be applied to dynamical and non-dynamical SR:

$$SNR = \frac{\varepsilon \Delta \mathrm{U}^2}{D} * \varepsilon^{-\Delta \mathrm{U}/\mathrm{D}}$$

Where ε is the input signal strength, D is the input noise intensity and ΔU is a constant related to the barrier height or the threshold of the system. To visualize the SR-effect, outcome performance (e.g. SNR) is typically plotted against noise intensity. A hallmark of the SR-effect is the inverted-U relationship between these two variables because a single maximum in the SNR occurs at a nonzero noise intensity. This relationship is due to the fact that, as previously stated, SR only occurs when an optimal level of noise is applied. This plot looks similar to a frequency dependent system in which the SNR is highest for a particular resonance frequency (see chapter 1 of (Rajasekar & Sanjuan)). This is the origin of 'resonance' in SR, however, this peak is noise-induced rather than frequency induced (Mark D McDonnell & Abbott, 2009).

Since the discovery of non-dynamical SR, the effect has been applied in different fields, including physics, mechanics and biology. With the increasing popularity of SR the definition has also broadened (Mark D McDonnell & Abbott, 2009). Whereas the original outcome measure was the SNR, residence time or switch rate, the broader definition is:

*Performance(noise + nonlinearity) > performance(nonlinearity)*

In this case ‘performance’ can be any performance measurement of interest, for example the percentage correct answers. The introduction of non-dynamical SR provided an avenue to investigate SR in excitable threshold systems, such as neural systems. In the next section, we will give an overview of the current state of knowledge on the SR-effect at the neurophysiological level.

## 1.2 SR at the neurophysiological level

The building blocks which process and transfer sensory information are neurons. Neurons are electrically excitable cells that transfer information from one neuron to the next via action potentials (APs). An AP is caused by a depolarization of the cell membrane of a neuron. In rest, a neuron maintains a voltage difference of -70 mV between the outside and the inside of the cell membrane. This is referred to as the rest-membrane potential. To keep the voltage difference at this level, sodium ions are actively pumped out of the cell. This requires energy in the form of adenine triphosphate (ATP). The cell exchanges three sodium ions for two potassium ions.

The cell membrane is impermeable to ions, and ions can only cross the membrane through voltage gated ion-channels. Most of the ion channels are closed when the cell is close to the rest-membrane threshold. When a stimulus arrives at the neuron, sodium channels will open. This will lead to an influx of sodium ions. When the stimulus is sufficiently strong then the membrane potential reaches a threshold, which is usually -55mV, and an AP will occur. The generation of APs is an all-or-nothing phenomenon, meaning that once the threshold is crossed there will always be an AP. This all-or-nothing phenomenon induces a non-linearity in most neuronal systems (Funke, Kerscher, & Worgotter, 2007). When the AP-generation threshold is reached, the system ‘jumps’ from the rest state to an excited state. The size of an AP is independent of the strength of the stimulus. The stimulus strength is coded by the frequency at which AP are generated (Gerstner, Kreiter, Markram, & Herz, 1997). The highest frequency that can be generated depends on the refractory period, that is, the time it takes for sodium-channels to recover and be activated again. The period it takes before a new AP can be induced in a typical animal neuron is 1-2 ms, which means that the highest frequency response can be 500 – 1000 Hz (Kandel, Schwartz, & Jessell, 2000).

Wiesenfeld and colleagues were one of the first to show a SR-effect in sensory neurons (K. Wiesenfeld et al., 1994). They recorded APs from the tailfin of a crayfish placed in water. The tailfin contains small hairs which are able to sense small movements in water. The SNR, which was obtained from power spectra, was found to increase when an optimal amount of random motion plus a periodic signal was added to the water. These findings have been replicated in sensory systems of different animals, such as in the multimodal sensory cells of sharks (H. A. Braun, Wissing, Schafer, & Hirsch, 1994), primary sensory neurons in the mouse dorsal root ganglia (Onorato et al., 2016) and in the cercal system of the cricket, which measures air motion as a defence mechanism (Levin & Miller, 1996). These experiments demonstrate that sensory neurons in different animals are sensitive to a SR mechanism by increasing the SNR of the signal at a neural level. A further study found that that small noise levels added to a weak stimulus increased the SNR of previously weak cortical visual responses in the primary visual cortex of cat (Funke et al., 2007). Interestingly, strong cortical responses to strong stimuli were only slightly reduced by the noise. The drop in the SNR when a certain noise level was applied was not a result of the increased background noise but due to fact that neurons become less sensitive to signal and noise. The authors suggest that this is a mechanism to prevent the build-up of too much noise.

The reviewed animal studies consistently added the noise and signal to the same receptor, which is referred to as a single-receptor design. This means that the signal may have already been enhanced at the receptor level in the peripheral nervous system (PNS). In order to avoid this possibly confounding factor in subsequent research, double receptor designs were utilised. In a double-receptor design the signal is added to a different receptor than the noise to eliminate the possibility that noise enhances the signal at the receptor level. An animal study using a double-receptor design applied a signal to one paw and noise to another paw in an anaesthetized cat. In this setup, the signal and noise interact for the first time in the spinal cord or somatosensory regions of the central nervous system (CNS). They found a SR-effect in spinal and cortical evoked field potentials (Manjarrez et al., 2003).

In humans, it is rarely possible to measure neuronal activity directly. The only time it is possible is with open surgery, for example, in patients with epilepsy (Engel, Pedley, & Aicardi, 2008). Therefore, we typically rely on indirect measurement techniques such as EEG. With EEG, the activity of many neurons is measured simultaneously. The amplitude or SNR of the EEG signal is dependent on the size and degree of activation of the activated neuronal networks, as well as on synchrony between responding neurons (Moss, 2004). In several studies SR-effects have been shown in the amplitude and SNR of human EEG signals in single and double-receptor designs (Lugo, Doti, & Faubert, 2008; Manjarrez, Diez-Martinez, Mendez, & Flores, 2002; Manjarrez, Mendez, Martinez, Flores, & Mirasso, 2007; Mendez-Balbuena et al., 2015; Srebro & Malladi, 1999). In these studies, a weak signal (subthreshold) is presented and different noise levels are added to the signal. The task for the participant is to detect the signal, whilst an EEG marker, such as the power of the EEG-signal, is used an outcome measurement. The results of such cross-modal studies (where the signal and noise first interact in the CNS) confirm it is possible to enhance a physiological signal in one modality by adding noise in a different modality (Lugo et al., 2008; Manjarrez et al., 2007; Mendez-Balbuena et al., 2015). These studies provide further support for the notion that central sensory processing is sensitive to a SR-effect. A question that remains open is whether the SR-effect induced in the nervous system is able to enhance behaviour.

## 1.3 SR at a behavioural level

One of the first experiments into SR-effects in animal behaviour was conducted with paddlefish. It was found that adding small amounts of electrical noise to the water increased the amount of available sensory information, which resulted in improved feeding behaviour (Russell, Wilkens, & Moss, 1999a). Behavioural SR-effects have also been observed in human behaviour using psychophysical techniques (Moss, 2004). These techniques allow for a quantitative investigation between a physical stimulus and human perception (Kingdom, Kingdom, & Prins, 2010). We will discuss these techniques in future chapters. In one of the first studies into behavioural SR in humans, participants were asked to detect a small indentation against their hand (Collins, Imhoff, & Grigg, 1996, 1997). The addition of mechanical noise to the indentation was found to increase detection performance, but only when the tactile stimulation was near the detection threshold and when an optimal level of noise was applied. Their results showed an inverted U-shape relationship between noise intensity and detection performance, a hallmark of the SR-effect. The behavioural SR-effect has also been demonstrated in different sensory modalities including audition (Zeng, Fu, & Morse, 2000) and vision (Simonotto, Riani, Seife, et al., 1997). These above-mentioned studies are single-receptor designs, where the noise can already enhance the signal at the receptor level. However, there is also behavioural evidence suggesting that SR can play a role in signal processing in the human CNS in studies that use a double-receptor design. For example, the

SR-effect can occur when one eye perceives a signal and the other eye perceives noise (Kitajo, Nozaki, Ward, & Yamamoto, 2003b). Other studies have found that it is possible to enhance detection performance on a perceptual detection task in one modality by applying noise to a different modality (Lugo et al., 2008; Manjarrez et al., 2007). In the multisensory perception literature it is believed that the signals from the different modalities interact for the first time in the CNS (Alais, Newell, & Mamassian, 2010).

In the studies reviewed above, the noise was always applied to a sensory receptor. The sensory receptor amplifies the signal and converts it into an electrical signal. However, biological noise is also present at the receptors level (Faisal et al., 2008). How the biological noise at the receptor level may interact with the externally applied noise is not known. One way to avoid this possible interaction is to add noise directly to the CNS. With the development of transcranial-random-noise-stimulation (tRNS) it has become possible to add noise to the CNS using well-defined characteristics (Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). The working mechanism of tRNS will be reviewed in a later section. The experiments presented in this thesis use tRNS to directly influence noise levels in the CNS. It is applied in combination with various behavioural paradigms to investigate whether central mechanisms of sensory perceptions are sensitive to a SR-effect.

This section summarized the evidence showing that a SR-effect can enhance behavioural performance. This enhancement in behavioural performance is likely due to an enhancement in the signal quality, however, in the next section we will see that other factors may also influence behavioural performance. Therefore, changes in detection performance do not necessarily mean that the sensory signal has changed. Below we will discuss in more depth psychophysical methods which are able to quantify the relationship between behavioural performance and the signal quality.

## 1.4 The relationship between signal strength and behaviour

Any behavioural detection task contains a decision component. In order to make a decision, the input signal has to be translated into a decision variable. This serves as an input for a classifier which determines if a signal was present based on the decision variable and on a suitable criterion (Tougaard, 2002). It is important to be able to distinguish the influence of noise on the signal quality from other processes involved in decision-making. Decision-making can be well described within the signal-detection-theory (SDT) framework (Green & Swets, 1974). SDT describes how we make decisions under uncertainty. This uncertainty can come from noise in the stimulus (external noise), for example, when it is very foggy on the road other cars will be difficult to see. That is, there is a lot of noise in the signal.  The uncertainty can also come from noise in the neuronal encoding of the stimulus. When you see the same stimulus multiple times, then the neuronal responses won't be exactly the same due to the noisy representation (biological noise) of the stimulus in the brain (Dean, 1981; Shadlen & Newsome, 1998). SDT assumes that due to this noise the internal response will vary randomly over trials around an average value. This produces a normal distribution of the internal representation of the stimulus. There is also a distribution for the internal representation of noise. How easy a stimulus can be distinguished from noise depends on the overlap of these two distributions. According to SR-theory adding noise could reduce this uncertainty by reducing the overlap between these two distributions.

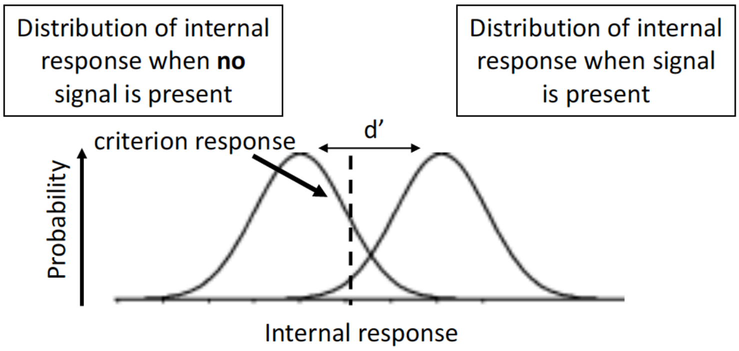

*Figure 1-3 Signal Detection Theory.*
In SDT the internal response of a signal is thought to follow a normal distribution. Separate distributions are displayed for the signal+noise (right distribution) and noise alone (left distribution). The less overlap between the distributions the easier it is to distinguish signal from noise. The measure of sensitivity in SDT is d' (d-prime), which represents how far apart the two distributions are. Adapted from (Heeger).

In SDT there are two main processes influencing decision-making performance: signal strength and decision criterion. Signal strength refers to the notion that stronger signals are easier to detect. Decision criterion reflects how willing a subject is to say that a signal is present when an ambiguous stimulus is presented. When a stimulus is very noisy a participant can decide to shift his criterion to the left, so the participant is less likely to say that the stimulus is present, which would mean that the detection performance goes up. However, this is not due to an enhancement in signal quality but rather due to a change in the participant's criterion. The goal of SDT is to distinguish the stimulus quality from the decision criterion. The measure of sensitivity used in SDT that is independent of the criterion value is d-prime (d'). Graphically this is represented as the distance between the two distributions (Figure 1-4). It depends on both the separation of the two distributions and their spread. It can be calculated when one knows the number of hits and falls alarms. A *hit* is when the participant indicates that the signal is present when it is present. A *false alarm* is when the participant indicates the signal is present when it is in fact absent. For completeness, we will also mention the two other possible outcomes: when the participant misses the stimulus this is classified as a *miss*, and when the participant correctly indicates that the stimulus was not presented this is classified as a *correct rejection*.

The formula to calculate d’ is:

$$d' = z(H) - z(F)$$

where z represents a z-transformation.

Whilst SDT is able to classify detection performance, it does not allow for a detailed explanation of the underlying processes involved in the actual decision process. One method of investigating the underlying cognitive processes involved in decision-making is with a drift-diffusion-model (DDM). This model is an extension on SDT because in addition to detection performance, it can also distinguish the quality of evidence informing the decision process (R. Ratcliff & McKoon, 2008). In the DDM stimulus evidence is collected over time from a starting point (*z*) until one of two boundaries is reached. The distance between these two boundaries, that is, how much evidence is needed for a response, is modelled by a parameter *a.* The rate at which the information is accumulated is the drift rate, *v.* The drift rate is dependent on the quality of the stimulus. The DDM has been very successful in describing human and animal behaviour (see (R. Ratcliff & McKoon, 2008; R. Ratcliff, Smith, Brown, & McKoon, 2016)).

## 1.5 Enhancing sensory perception

In this thesis we will investigate if central mechanisms of sensory information processing can be influenced by adding noise to the CNS. According to a SR-account, adding small amounts of noise should enhance information processing in the brain. This type of enhancement can be viewed as cognitive enhancement (Sandberg & Bostrom, 2006). The enhancement of cognition is not a new concept, since many different methods are already being tested and used by a large part of the population (Kelly, 2015; MacLean et al., 2010; Sandberg & Bostrom, 2006). Here, we will review some examples of pharmacological and non- pharmacological methods to enhance cognition and reflect on the different approaches. Two examples of widespread substances with a cognitive enhancing effect are caffeine, an adenosine receptor antagonist, and nicotine, a nicotinic cholinergic receptors agonist (Lorist & Snel, 1997a; Rusted, Trawley, Heath, Kettle, & Walker, 2005). Caffeine is able to improve reaction times (Lorist & Snel, 1997b), facilitate perceptual processing (Ruijter, de Ruiter, Snel, & Lorist, 2000; Smith, Brice, Nash, Rich, & Nutt, 2003) and strengthen action monitoring (Tieges, Richard Ridderinkhof, Snel, & Kok, 2004). The neurophysiological mechanism underlying these behavioural improvements is a blockage of the inhibitory adenosine $A_1$ (located in cortical layers and striatum) and $A_{2A}$ (located in the striatum) receptors by caffeine. Besides caffeine, nicotine is also a substance that can be used to improve cognitive functioning. Nicotine can for example enhance selective attention, recognition and working memory, however there are no reports of a perceptual enhancement induced by nicotine. The neurophysiological mechanism causing the cognitive enhancement is a binding of nicotine on the nicotine cholinergic receptors, which are widespread through the brain (Brody et al., 2004; D'Souza & Markou, 2011). Besides the positive effects on cognition the intake of nicotine is also associated with negative health effects (Swan & Lessov-Schlaggar, 2007) . Caffeine doesn't seem to have negative side effects, as long as it is not consumed in excessive amounts (Nawrot et al., 2003; Smith, 2002), however the benefits of caffeine decline over time and with chronic use (McIntire, McKinley, Goodyear, & Nelson, 2014), which might make non-invasive brain stimulation (NIBS) an attractive alternative.

Cognitive enhancement can also be achieved with non-pharmacological interventions such as meditation and non-invasive brain stimulation methods (see (Kelly, 2015; MacLean et al., 2010; Sandberg & Bostrom, 2006) for a review on various methods of cognitive enhancement). For example, it has been shown that meditation training resulted in medium effect sizes on attention and small effects on memory performance (Sedlmeier et al., 2012). More interestingly, intensive meditation training (a few hours each day for 3 months) has been suggested to improve perceptual discrimination performance (cohen's $d = 0.63$ (Hankey, 2006; MacLean et al., 2010)). It has been shown in studies with Tibetan monks that performance on various cognitive tasks is better compared to participants with no meditation experience. The underlying mechanism might be a larger effectiveness of information processing during cognitive tasks in the monks compared to participants without meditation experience (Fries, 2005; Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). The mastering of meditation requires much time and commitment, which is not required with NIBS, making it an attractive alternative to meditation training.

A new and popular method which could instantaneously enhance cognitive performance is NIBS. Currently, a considerable amount of research is being performed to understand the effects of NIBS on perception (see (Luber & Lisanby, 2014) for a review on cognitive enhancement with TMS). It has been demonstrated that Transcranial Magnetic Stimulation (TMS) is able to enhance performance by around 10% (Cohen's d = 0.47) on a visual contrast detection task (Abrahamyan, Clifford, Arabzadeh, & Harris, 2015) and by a similar amount on a visual decision making task (Schwarzkopf, Silvanto, & Rees, 2011). Improvements in visual detection performance have also been observed by applying weak currents to the brain directly with transcranial Current Stimulation (tCS) (Dresler et al., 2013). It has been suggested that the above-mentioned effects of NIBS on detection performance can be explained by a SR-effect (C. Miniussi, Harris, & Ruzzoli, 2013). In the current thesis, we will investigate this further by adding noise to the brain directly with transcranial random noise stimulation (tRNS).

## 1.6 Transcranial-random noise stimulation (tRNS)

tRNS is a method of applying noise at the neuronal level rather than to peripheral receptors. This approach is critical in order to understand whether noise added to central sensory processing is able to induce a SR-effect at a behavioural level. tRNS is a type of tACS (transcranial alternating-current stimulation) where a mix of frequencies is applied. The frequencies that are applied are usually between 0.1 and 640 Hz, which is the high end of physiologically measured human brain oscillations (Gobbele et al., 2000). It generates a random level of current for each sample of the signal. These random current levels are normally distributed. Therefore, an intensity of 1 mA indicates that 99% of all generated samples lay between 0.5 mA and -0.5 mA. This results in noise with the same characteristic as is used in behavioural SR-experiments (zero-mean Gaussian white noise).

The working mechanism of tRNS is not completely understood, however, it has been suggested that tRNS can enhance the recruitment of voltage-gated sodium channels in response to depolarizing currents (Terney et al., 2008). This is supported by animal work where the application of repetitive extracellular high frequency stimulation in rat neurons led to an inward flow of sodium, which caused a weak depolarization of the cell membrane (Bromm, 1968; Schoen & Fromherz, 2008). Chaieb, Antal, & Paulus (2015) demonstrated that the effect of tRNS is sodium channel dependent by administering a sodium antagonist which abolished after-effects of tRNS on cortical excitability changes (Chaieb, Antal, & Paulus, 2015). The suggested underlying working mechanism of tRNS is that it can open voltage-gated sodium channels repetitively, which leads to a sodium influx. It is important to note that tRNS doesn't possess a DC component, and therefore does not modify the transmembrane potential directly (Bindman, Lippold, & Redfearn, 1964; Terney et al., 2008). When tRNS is applied continuously, it is likely that after 3 minutes long-term potentiation (LTP)-mechanisms start to occur (Terney et al., 2008), which is the likely reason that after effects on motor cortex excitability and behaviour are observed. LTP is a strengthening of synapses based on recent patterns of activity (Purves et al., 2001), that is, a plasticity effect.

Another possible working mechanism of tRNS is that it might increase neuronal synchronization between different brain areas (L. M. Ward, Doesburg, Kitajo, MacLean, & Roggeveen, 2006; L. M. Ward, MacLean, & Kirschner, 2010). This idea is supported by a fMRI study where tRNS was applied for four minutes over M1 before a motor task (finger-tapping) (Chaieb et al., 2009). They found a decrease in cortical activity during finger tapping after application of tRNS compared to sham stimulation. Similar results have been reported by a different group (Saiote, Polania, Rosenberger, Paulus, & Antal, 2013). It is suggested that high frequency tRNS increases neuronal synchronization, which is reflected by a decrease in the BOLD signal (Goldman, Stern, Engel, & Cohen, 2002; Singh, Barnes, Hillebrand, Forde, & Williams, 2002).

Application of tRNS for an extended period of time has been demonstrated to increase cortical excitability for at least 60 minutes after stimulation (Terney et al., 2008). Prolonged application of tRNS can also influence human behaviour. For example, tRNS application during a perceptual learning task has been demonstrated to improve learning performance (Fertonani, Pirulli, & Miniussi, 2011). While the authors speculated that SR was a possible underlying reason for improved performance, this could not be confirmed due to the study design. They could not distinguish between a pure stochastic resonance effect and changes induced by neural plasticity. In these studies, high-frequency tRNS (101 – 640 Hz) was more effective in inducing effects compared to low frequency tRNS (0 – 100 Hz). This may be because the time constant of cell bodies and dendrites is between 1 and 10 milliseconds (Kandel et al., 2000). Therefore, stimulating between 100 and 1000 Hz (a period of between 0.01 and 0.001sec.) would be optimal to influence neuronal processing. The work presented in this thesis focused only on the online-effects of tRNS. Therefore, in each study measures were in place to minimize possible LTP-effects induced by tRNS.

## 1.7 Motivation

As discussed, it has been demonstrated that the performance of animals and humans on various tasks can be enhanced when small amounts of noise are added to the peripheral nervous system (Hanggi, 2002) both in single- and double-receptor designs. The SR-effect has applications in the medical field, e.g. in cochlear implants to enhance the signal quality (Zeng et al., 2000), and in shoe insoles to improve balance performance (Priplata, Niemi, Harry, Lipsitz, & Collins, 2003). The question that still remains is whether the SR-effect can also be induced in the human brain when noise is added to the central nervous system directly with tRNS. The value of the results is not only in a better understanding of the counterintuitive SR-phenomenon, but also an improved insight into the neurophysiology of sensory processing and extended knowledge of the possibilities and limitations of tRNS for research and clinical purposes.

## 1.8 Chapter overview

The main goal of this thesis is to investigate if central processing of visual information is sensitive to a SR-mechanism.

### *1.7.1 Chapter 2*

In this chapter we investigate if detection performance can be enhanced by applying tRNS, in accordance with the non-dynamical SR-effect. tRNS is applied to the visual cortex while participants perform a visual detection task. Modelling is used to estimate the electrical field strength in the visual cortex.

### *1.7.2 Chapter 3*

In this chapter, a perceptual decision-making task is used to investigate whether higher order cortical areas involved in decision-making processes are sensitive to a SR-effect. tRNS is applied to the visual cortex to investigate if performance can be enhanced. A computational model is employed to investigate which stages of the decision-making process are influenced by tRNS.

### *1.7.3 Chapter 4*

After demonstrating that tRNS can induce a SR-effect in line with the non-dynamical SR theory in Chapters two and three, this chapter investigates if a SR-effect according to the dynamical-

SR theory can be induced with tRNS. Binocular rivalry is used to test this idea. Binocular rivalry is a task in which the brain is in a dynamical state.

### *1.7.4 Chapter 5*

In this chapter the main findings are summarized, and the results and implications in light of the broader literature are discussed, including SR and non-invasive brain stimulation literature.

# Chapter 2: Transcranial Random Noise Stimulation of Visual Cortex: Stochastic Resonance Enhances Central Mechanisms of Perception

## 2.1 Abstract

Random noise enhances the detectability of weak signals in nonlinear systems, a phenomenon known as stochastic resonance (SR). Even though counter-intuitive at first, SR has been demonstrated in a variety of naturally occurring processes, including human perception where it has been shown that adding noise directly to weak visual, tactile or auditory stimuli enhances detection performance. These results indicate that random noise can push subthreshold receptor potentials across the transfer threshold, causing action potentials in an otherwise silent afference. Despite the wealth of evidence demonstrating SR for noise added to a stimulus, relatively few studies have explored whether or not noise added directly to cortical networks enhances sensory detection. Here we administered transcranial random noise stimulation (tRNS, 100-640 Hz zero-mean Gaussian white noise) to the occipital region of human participants. For increasing tRNS intensities (ranging from 0 to 1.5 mA) the detection accuracy of a visual stimuli changed according to an inverted U-shape function, typical of the SR phenomenon. When the optimal level of noise was added to visual cortex, detection performance improved significantly relative to a zero noise condition (9.7 ± 4.6%) and to a similar extent as optimal noise added to the visual stimuli (11.2 ± 4.7%). Our results demonstrate that adding noise to cortical networks can improve human behaviour and that tRNS is an appropriate tool to exploit this mechanism.

Author contributions:

*Onno van der Groen:* Experimental design, Data collection, Data analysis and interpretation, Drafting of the manuscript
*Prof. Nicole Wenderoth:* Experimental design, Provided revisions to manuscript
*Dr. Daniel Woolley:* Provided revisions to the manuscript

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### *2.1.1 Significance statement*

Our findings suggest that neural processing at the network level exhibits non-linear system properties that are sensitive to the stochastic resonance phenomenon and highlight the usefulness of tRNS as a tool to modulate human behaviour. Since tRNS can be applied to all cortical areas, exploiting the SR phenomenon is not restricted to the perceptual domain but can be utilised for other functions that depend on non-linear neural dynamics (e.g. decision-making, task switching, response inhibition and many other processes). This will open new avenues for using tRNS to investigate brain function and enhance the behaviour of healthy individuals or patients.

## 2.2 Introduction

Noise is as an intrinsic property of all biological systems and is typically viewed as being detrimental for neural computations and the associated behaviour. However, when an appropriate level of random noise is added to a *nonlinear system* it can enhance weak signals, an effect known as stochastic resonance (SR). For example, adding an optimal level of noise to weak visual (Riani & Simonotto, 1994; Simonotto, Riani, Seife, et al., 1997; Lawrence M Ward, Desai, Rootman, Tata, & Moss, 2001), tactile (Collins, Chow, & Imhoff, 1995; Collins et al., 1996) or auditory stimuli (Zeng et al., 2000) has been shown to significantly enhance detection performance. SR is characterized by a larger effect for subthreshold stimuli than for suprathreshold stimuli (Gingl, Kiss, & Moss, 1995), and the signal enhancing effect depends on the intensity of the added noise according to an inverted U-shape curve. The inverted U-shape curve is a hallmark of the SR phenomenon and indicates that the level of added noise needs to be optimal in order to maximally enhance performance.

Most previous studies added noise to the stimulus (single receptor design) so that signal and noise could already interact in the peripheral nervous system, which contains non-linear neural elements like sensory receptors. However, SR-effects are certainly not limited to the peripheral nervous system. For example, it has been shown that visual detection performance can be enhanced by adding visual noise to one eye and a subthreshold visual signal to the other (Kitajo et al., 2003b). This suggests that neural processing is sensitive to the SR phenomenon. However, it is not clear whether it emerges at the cortical or sub-cortical level because inputs from both eyes interact in the lateral geniculate nucleus (LGN) of the thalamus (Tong, Meng, & Blake, 2006; Wunderlich, Schneider, & Kastner, 2005) and primary visual cortex.

With the recent development of transcranial random noise stimulation (tRNS) (Chaieb et al., 2015; Terney et al., 2008) it is now possible to add noise to the cortex with well-controlled frequency, duration and intensity characteristics. Although the physiological mechanism of tRNS is not completely understood, it has been demonstrated that a short period of repetitive extracellular high frequency stimulation in rat neurons resulted in an inward sodium current, which caused a weak depolarization of the cell membrane (Bromm, 1968; Schoen & Fromherz, 2008). Previous work in humans has demonstrated physiological and behavioural after-effects following prolonged tRNS stimulation (Fertonani et al., 2011; Terney et al., 2008). For example, 10 minutes of tRNS increased the cortical excitability for up to an hour after stimulation (Terney et al., 2008) and ~22 minutes of tRNS during a perceptual learning task improved behavioural performance (Fertonani et al., 2011). In these studies it has been suggested that SR plays a role in tRNS but this has not been tested directly. Importantly, if tRNS can influence behaviour via a SR mechanism the effect should be observable online and dependent on the noise and stimulus intensity. In the present study we tested if visual detection performance can be enhanced in a SR-like manner when different noise intensities are applied to the visual cortex while performing a visual detection task of varying difficulty.

First, we replicated previous studies by testing if adding noise to the visual stimulus directly (Visual-Noise experiment) enhances detection performance in a manner consistent with the SR phenomenon. We then tested if adding noise to the visual cortex with tRNS (tRNS-Noise experiment) enhances visual detection performance. Finally, we applied tRNS to the forehead (i.e. over frontal lobe) to determine if it has unspecific effects on detection performance (tRNS-Control experiment). We predicted that the addition of noise would improve the detection of subthreshold stimuli more than suprathreshold stimuli in both the Visual-Noise and tRNS-Noise experiments, but not in the tRNS-Control experiment. For both Visual-Noise and tRNS-Noise, we expected to find an inverted U-shape relationship between noise intensity and detection performance, indicating that performance is only enhanced when an optimal level of noise is added.

## 2.3 Material and Methods

*2.3.1 Power analysis and subjects*

An a priori power analysis (G*Power v3.1.3, (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that a sample size of 7 subjects per group would be sufficient to detect a significant effect on detection performance in the Visual-Noise experiment with a power of 0.80 for an alpha level of 0.05. These values are based on previous work investigating the effect of noise on the detection of a subthreshold visual signal (Sasaki et al., 2008). In that study noise added directly to the visual stimulus had a large effect on signal detection (Cohen's d = 1.71, n = 19). In our experiments we included more subjects to ensure sufficient power in the tRNS experiments, since it was not possible to estimate the effect of tRNS on a visual detection task.

A total of fifty-two healthy right-handed subjects took part in at least one out of three separate experiments (26 female; mean age 24; age range 18-30). All subjects had normal or corrected-to-normal vision and met the inclusion criteria for tRNS. Subjects were allowed to participate in different experiments but we ensured that experimental sessions were separated by at least 24 hours and that the order of participating in different experiments was counterbalanced (below detailed descriptions of subject characteristics are reported for each experiment separately).

The study was approved by the Human Research Ethics Committee, ETH Zürich (EK 2013-N-55) and the Kantonale Ethik Komission Zürich, Switzerland (KEK-ZH-Nr. 2014-0269). Informed consent was obtained from all participants before the start of the experiment.

*2.3.2 Stimulus and apparatus*

All experiments took place in a dark and quiet room. Participants were seated 1 m away from a screen on a comfortable chair. Visual stimuli were generated using Matlab version 2012b (Natick, MA, 2010a) and the Psychophysics toolbox (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997). Stimuli were presented on a Sony CPD-G420 colour monitor with a calibrated linearized output at a resolution of 1280x1024 pixels and a refresh rate of 75 Hz. The visual target stimulus was a vertically orientated Gabor patch (a sinusoidal luminance pattern presented within a Gaussian envelope) in a soft circular aperture with a vertical orientation. The target extended a visual angle of 1.4°, with a spatial frequency of 5 cycles per degree, and a mean luminance of 52 cd/m$^2$. Stimuli were presented on a uniform grey background (52 cd/m$^2$). The Gabor patch was always presented within one of eight locations (indicated by white circles on the screen, 1.5° visual angle), which were positioned around the fixation cross (0.6° visual angle) as shown in Figure 2-1A. The stimuli and apparatus were the same for all three experiments.

### *2.3.3 Two-interval forced choice (2-IFC) visual detection task*

In all three experiments participants performed a 2-IFC visual detection task. Each trial started with a green fixation cross (visual angle 0.6°). After a key press there was a beep and 8 circles appeared for 2.04 seconds at potential target locations on the screen (first interval). Then a blank screen was shown for 1 s and the 8 circles reappeared for another 2.04s (second interval). Subjects were instructed that the visual target stimulus (Gabor patch) was presented at one of the 8 potential locations either during the first or second interval. After the second interval ended the fixation cross turned red prompting subjects to make a forced-choice judgment to indicate which interval contained the visual target. After participants responded there was a break of 3 seconds before the next trial started. The target was presented the same number of times at each of the 8 possible locations to account for the possibility that detection performance may be location dependent (Figure 2-1A). Furthermore, all presentation locations were situated on the non-cardinal axes since it has been shown that detection performance on these axes does not vary greatly compared to detection performance on the cardinal axes (Cameron, Tai, & Carrasco, 2002), We used a Tobii eyetracker (model tx300, Sampling frequency 300 Hz) to control for eye-movements and blinks during stimulus presentation in both the thresholding block and the main experiment. When eye-movements or blinks were detected, the trial was repeated. In all experiments participants performed 5 blocks of 40 trials, with a different noise intensity tested in each block. The detection task was the same in all three experiments, however, in the Visual-Noise experiment noise was added to all 8 circles on the screen and in the tRNS-Noise and tRNS-Control experiments noise was applied via tRNS.

### *2.3.4 Determining individual target stimulus intensities*

At the start of each experiment we determined each individual's target contrast detection threshold with a thresholding block. In the thresholding block the same 2-IFC task was used as in the main experiment without presentation of any noise but the intensity of the grating was adapted to determine the visual detection threshold of each subject. We determined the stimulus contrast that corresponded to 75% detection accuracy during the 2-IFC task using a QUEST staircase procedure (thresholding block) (A. B. Watson & Pelli, 1983).

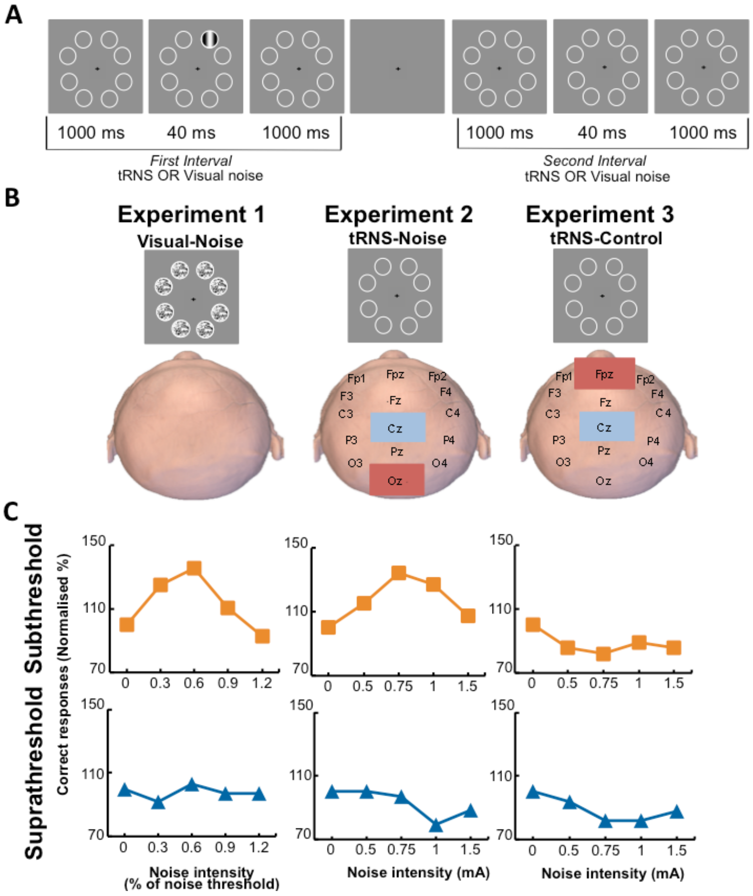

*Figure 2-1 Experimental setup.*
**A)** Two-alternative forced choice (2-IFC) visual detection task. Subjects fixated on the centre of the screen and a visual stimulus was randomly presented either in the first (shown here) or second interval. After the second interval participant had to indicate which interval contained the stimulus. In the main experiment the stimulus contrast was fixed to yield either 60% detection accuracy (subthreshold group) or 80% detection accuracy (suprathreshold group). **B)** Representation of the three different experiments. Note that in the tRNS-Noise and tRNS-Control experiments no noise was presented on the screen. **C)** Representative data of individual participants. The participants in the Visual-Noise(left panel) and tRNS-Noise (middle panel) experiment show a peak in their detection performance when noise is added to a subthreshold stimulus (orange line) but not to a suprathreshold stimulus (blue line).

The thresholding block started by determining a rough estimate of the participant's detection threshold value with a simple up-down staircase method. After five reversals of their yes-no responses, we stopped the staircase and calculated an estimate of the individual detection threshold, which we used as an input for the QUEST. Then two QUEST staircases were randomly interleaved, one that started at 1.2 times the estimated threshold, and one at 0.8 times the estimated threshold (40 trials per QUEST). The stimulus contrast was adjusted to yield either 60% detection accuracy (subthreshold group) or 80% detection accuracy (suprathreshold group) and was fixed at this value in the main experiment. The procedure to determine individual target stimuli intensities was conducted at the start of every experiment.

### *2.3.5 Experiment 1: Visual-Noise Experiment*

In this experiment we tested the hypothesis that adding an optimal level of noise to a subthreshold visual target stimulus can improve visual contrast sensitivity. Participants (n= 31; 14 females; mean age 24; age range 19-30) were randomly assigned to one of two groups and performed a 2-IFC visual detection task (Figure 2-1A). One group detected the visual target stimulus presented at a subthreshold contrast level (corresponding to an average detection accuracy of 60%) and the other group detected the visual target stimulus presented at a suprathreshold contrast level (corresponding to an average detection accuracy of 80%).

Visual noise was added together with the visual stimulus on the screen (Visual-Noise experiment, Figure 2-2) and the noise intensity varied between 0, 0.3, 0.6, 0.9 and 1.2 times the individual noise threshold. In this experiment participants completed an additional block of thresholding in which a QUEST staircase was used to determine a 75% noise detection threshold. The procedure was the same as for determining individual target stimulus intensities, however, the target was replaced with random Gaussian white noise, which was presented for one complete interval duration (2.04 s) at all eight locations.

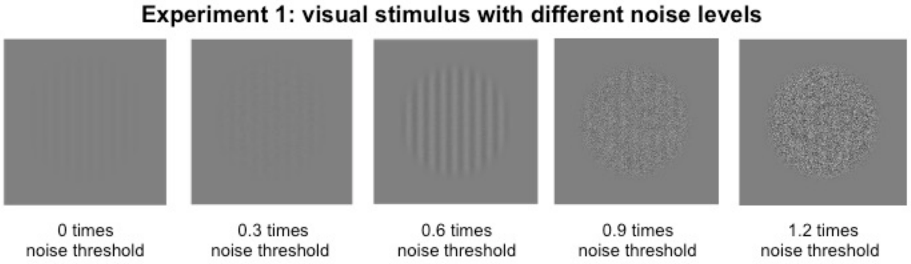

*Figure 2-2 Example of a visual target stimulus with different noise levels.*
*In the Visual-Noise experiment different levels of noise (multiples of individual noise detection thresholds) were added to the target stimulus.*

### *2.3.6 Experiment 2: tRNS-Noise Experiment*

In this experiment we tested the hypothesis that applying tRNS to the occipital cortex at an optimal intensity can improve the visual contrast sensitivity of a subthreshold visual stimulus. Participants (n = 38; 21 females; mean age 25; age range 19-30) were randomly assigned to one of two groups (subthreshold or suprathreshold contrast levels) and performed a 2-IFC visual detection task (Figure 2-1A). The target stimulus intensity and visual detection task used were the same as for the Visual-Noise experiment, except that noise was applied via tRNS to the occipital cortex during visual stimulus presentation (tRNS-Noise).

In this experiment randomly alternating current (frequencies between 100-640 Hz) of 0, 0.5, 0.75, 1 or 1.5 mA intensity (amplitude) with a 0-mA offset was applied during both intervals of the 2-IFC task for 2.04 s each. No noise thresholding block was conducted because it is not possible to determine individual noise levels for tRNS noise. Noise was injected centrally with tRNS applied to the visual cortex. Electrode placement was determined using the 10-20 system. The stimulation electrode was placed over the occipital region (Oz in the 10-20 EEG system) and the reference over the vertex (Cz in the 10-20 EEG system, see Figure 2-1B). This setup is suitable for stimulation of the visual cortex (Neuling, Wagner, Wolters, Zaehle, & Herrmann, 2012). Electroconductive gel was applied to the contact side of the electrode (5x7 cm) to reduce skin impedance. Electrodes were held in place with a bandage. Stimulation was delivered by a battery-driven electrical stimulator (Version DC-Stimulator-Plus, neuroConn). The maximum current density in this study was 42.85 $\mu A/cm^2$, which is within recently updated safety limits (Fertonani, Ferrari, & Miniussi, 2015). The tRNS waveform was created in Matlab and sent to the DC-stimulator via a data acquisition card (DAQ, NI usb 6343 x series). Modelling was used to estimate the electrical field strength in the visual cortex (Spheres 2.0 (Truong et al., 2014)). We did this for every tRNS intensity and for specific frequencies between 100 and 500 Hz (50 Hz steps, see table 1).

*Table 2-1 Modelled electric field strength (V/m) for different transcranial electrical current stimulation (tECSs) intensities (mA) and frequencies (Hz).*
*The modelling shows that that all stimulation frequencies were transmitted to the brain and that the current applied is strong enough to reach the cortex (scaling quasi-linearly with tRNS intensity).*

| | *Intensity(mA)* | | | |
|---|---|---|---|---|
| *Frequency (HZ)* | *0.5 mA* | *0.75 mA* | *1 mA* | *1.5 mA* |
| *100 Hz* | 0.7 V/m | 1.6 V/m | 2.2 V/m | 3.2 V/m |
| *150 Hz* | 0.8 V/m | 1.5 V/m | 2 V/m | 3.1 V/m |
| *200 Hz* | 1.1 V/m | 1.5 V/m | 2.2 V/m | 3.1 V/m |
| *250 Hz* | 1 V/m | 1.6 V/m | 2.2 V/m | 3 V/m |
| *300 Hz* | 1 V/m | 1.6 V/m | 2.1 V/m | 3 V/m |
| *350 HZ* | 1 V/m | 1.5 V/m | 2.1 V/m | 3 V/m |
| *400 Hz* | 1 V/m | 1.5 V/m | 2.1 V/m | 3 V/m |
| *450 Hz* | 1 V/m | 1.5 V/m | 2.2 V/m | 3 V/m |
| *500 Hz* | 1 V/m | 1.5 V/m | 2.2 V/m | 3 V/m |

### *2.3.7 Experiment 3: tRNS-Control Experiment*

This experiment served as a control to test for unspecific effects of tRNS on visual detection performance. We tested if tRNS applied to the forehead can improve the visual contrast sensitivity of a subthreshold visual stimulus. In this experiment participants (n= 20; 9 females;

mean age 25; age range 21-30) were randomly assigned to one of the two groups and performed the 2-IFC visual detection task (Figure 2-1). This experiment followed the same procedure as the tRNS-Noise experiment, with the only difference being that the stimulation electrode was placed over the forehead and the reference electrode over the vertex (Cz in the 10-20 EEG system). The noise was again applied in both intervals for 2.04 seconds.

## 2.4 Data Analyses

The same statistical procedures were applied to all three experiments. The alpha level was set to 0.05 for all tests.

To quantify the SR-effect we normalized the %Corr detection performance to the zero noise condition (all trials where no noise was applied):

$$\%Corr(normalized) = \frac{\%Corr(i)}{\%Corr(zero\ noise)}$$

with i denoting each of the 5 tested noise intensities. To test for effects of added noise on detection performance, normalized accuracy data were subjected to a repeated measures analysis of variance (ANOVA) with the within subjects factor *Noise Intensity* (5 levels for each experiment) and the between subjects factor *Stimulus Intensity* (subthreshold vs suprathreshold group). Additionally, pre-planned comparisons testing performance for each noise level against the zero noise condition were conducted and corrected for multiple comparisons, resulting in an adjusted alpha level of 0.0125. It is well known that there are big individual differences in optimal noise levels (Collins et al., 1996; Martinez, Perez, Mirasso, & Manjarrez, 2007). Therefore we determined the optimal noise level for each participant, which was defined as the noise level where detection performance was best. The difference in performance between an individual's optimal noise level (i.e. the peak in each graph in Figure 2-1C) and zero noise performance (i.e. the first data point in each graph in Figure 2-1C) served as a measure of the effectiveness of optimal noise (maximum improvement). Note that a maximum improvement of 0 indicates that there was no SR-effect, i.e. adding noise always led to worse performance. Statistical analyses were performed using SPSS (Version 20.0, Armonk, NY: IBM Corp.). Finally, we calculated the effect size of the noise induced performance improvements for each of the three different experiments (see table 2). We also determined that the actual statistical power of our main experiments was around 0.6 (G*Power v3.1.3, (Faul et al., 2007).

*Table 2-2 Overview of effect sizes and obtained statistical power for the influence of noise on detection performance in the different experiments.*
The effect sizes are based on the maximum improvement data for each experiment. This was done for the initial and control analyses

| | Effect sizes (Cohen's d) | | Obtained power | |
|---|---|---|---|---|
| *Experiment* | Initial Analysis | Control Analysis | Initial Analysis | Control Analysis |
| *Visual-Noise* | 1.15 | 0.94 | 0.85 | 0.68 |
| *tRNS-Noise* | 0.81 | 0.77 | 0.65 | 0.59 |
| *tRNS-Control* | 0.05 | 0.24 | 0.05 | 0.08 |

### *2.4.1 Additional analyses*

The goal of this additional analysis was to determine the optimal noise level and the associated performance improvement using independent datasets. Therefore, all trials per subject and per noise level were randomly split in half. One half of the trials (discovery data set) was used to define the optimal noise level (i.e. the noise value which causes a maximum improvement in detection performance) and the other half (test data set) for determining the performance improvement observed for the "discovered" optimal noise level when compared to zero noise performance. In this way determining the optimal noise level and obtaining the associated performance improvement are based on independent data. This procedure was done for all experiments and for all noise levels. The procedure was repeated 1000 times for each participant yielding an average performance improvement associated with the optimal noise level and these values were subsequently compared between the sub- and suprathreshold groups using the same statistics as described above.

## 2.5 Results

### *2.5.1 Visual noise added to the visual stimulus improves detection*

In the Visual-Noise experiment we investigated the influence of adding different levels of visual noise (i.e. presented together with the visual stimulus on the screen) on the detection of either subthreshold or suprathreshold stimuli. Two participants were excluded from the analysis in the subthreshold group because they performed below chance level in the zero noise condition. This left a total number of 29 participants in the analyses (15 in the subthreshold group).

Adding noise to the visual stimulus improved detection accuracy significantly more in the subthreshold stimuli group than in the suprathreshold stimulus group (Figure 2-3A, significant *Group* main effect tested with a repeated measures ANOVA, F(1,27) = 4.59, p = 0.041). When noise was added to subthreshold stimuli, normalized detection accuracy improved gradually for low to medium noise levels. However, when too much noise was added detection accuracy deteriorated again. Thus, an inverted U-shape function was observed when detection accuracy was expressed as a function of the noise intensity, both at the individual (see Figure 2-1C (orange line first column) for a representative subject) and group level (Figure 2-3A, orange line). This pattern of behaviour is typical for the SR phenomenon. By contrast, when noise was added to suprathreshold stimuli, detection performance was nearly unchanged (Figure 2-1C (blue line first column) and Figure 2-3A, blue line). Group differences were most pronounced when noise intensity corresponded to 0.6 times the individual noise detection threshold, however, statistical significance was only reached at an uncorrected level (t(14) = 2.48, p = 0.026, pre-planned comparisons, corrected alpha level = 0.0125).  This is likely due to high inter-individual variability in optimal noise levels, which has also been reported in other SR studies (Collins et al., 1996; Martinez et al., 2007). Therefore we looked at whether individual participants differed regarding their “optimal” noise level, defined as the noise intensity that led to maximal detection accuracy. Figure 2-3B shows the distribution of optimal noise levels for the subthreshold (orange) and suprathreshold groups (blue). In the subthreshold group most, but not all, participants benefited from the 0.6 noise level. In contrast, the participants in the suprathreshold group benefited most from 0 noise, indicating that adding noise to suprathreshold stimuli resulted in poorer detection performance in most cases. We also analysed the maximum improvement of each participant compared to the zero noise condition (Figure 2-3C) and found that the greatest noise-induced improvement in accuracy (% change relative to zero noise condition) was significantly larger in the subthreshold group (15.7%) then the suprathreshold group (5.5%, t(27) = 3.10, p = 0.005). Note, however, that the above analysis contains an element of intrinsic circularity because the optimal noise level and the maximal improvement of each individual were based on the same dataset. While this procedure is unlikely to compromise the between group comparison, it certainly overestimates the size of the stochastic resonance effect in the Visual-Noise experiment. We therefore performed a control analysis that determined the optimal noise level and the associated detection performance improvement independently. This control analysis confirmed that adding an optimal level of visual noise to subthreshold stimuli improved detection accuracy by 12.04%, which is significantly larger than adding noise to suprathreshold stimuli (12.04 vs 3.70, t(21.981) = 2.563, *p = 0.018,* see Table 3 for an overview of the maximum improvement and optimal noise levels for all experiments and both analyses). Effect size analyses revealed that adding noise had a large effect on detection performance when the subthreshold stimuli group was compared to the suprathreshold stimuli group (table 2). Finally, we found a significant correlation between absolute detection accuracy in the zero noise condition and the maximum noise-induced improvement (r(27) = -0.68, p < 0.001, Figure 2-3D). Thus, participants who had to detect a visual stimulus below their detection threshold benefit more from added noise than participants that had to detect a visual stimulus at or just above their detection threshold (Figure 2-3D).

One general concern is that the results of the suprathreshold group might have been confounded by a ceiling effect. However, only 1 participant in the suprathreshold group reached 100% accuracy when noise was added to the stimuli and this participant's maximum improvement (17%) clearly exceeded the group mean of 5.5%. In summary, we replicated and extended previous findings showing that SR-effects are significantly larger for subthreshold than for suprathreshold stimuli using a conventional paradigm that adds visual noise to a visual detection task.

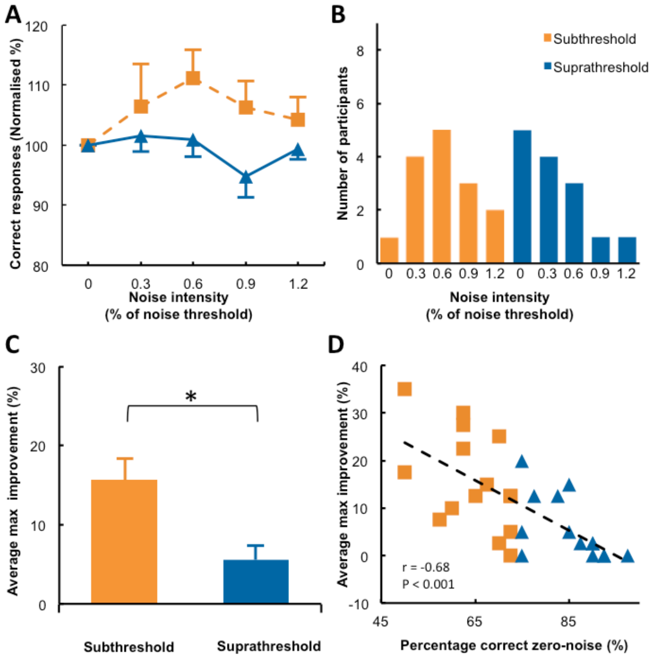

*Figure 2-3 Results when noise is added to the visual stimulus.*
**A)** Detection accuracy relative to the zero noise condition is shown for each noise level in the subthreshold and suprathreshold stimulus groups. **B)** Distribution of the individual optimal noise levels (defined as the noise intensity that yields maximum accuracy detection). **C)** A comparison between the average maximum improvement (i.e. the % difference between maximum accuracy and zero noise accuracy) showed a significant difference between the subthreshold and suprathreshold groups (* p < 0.05). **D)** We found a significant correlation between baseline performance and maximal improvement, indicating that participants with low detection accuracy in the zero noise condition benefited most from adding optimal noise. Error bars indicate standard errors.

*Table 2-3 Overview of the maximum improvement and optimal noise levels for the different experiments and different analysis.* The results of our additional analysis confirmed the results of our optimal noise level analysis even though the performance improvement observed for the optimal noise level is, as expected, smaller in our additional analysis.

| | Initial Analysis | | Control Analysis | |
|---|---|---|---|---|
| Experiment | Optimal noise Level mode | Max improvement (%) mean ± std error | Optimal noise Level mode | Max improvement (%) mean ± std error |
| *Subthreshold* | | | | |
| *Visual-Noise* | 60% of noise threshold | 15.67 ± 2.69 | 60% of noise threshold | 12.04 ± 2.83 |
| *tRNS-Noise* | 1 mA | 14.38 ± 2.41 | 1 mA | 11.07 ± 2.27 |
| *tRNS-Control* | 0 mA | 5 ± 2.01 | 0 mA | 2.45 ± 1.65 |
| *Suprathreshold* | | | | |
| *Visual-Noise* | 0% of noise threshold | 5.53 ± 1.78 | 30% of noise threshold | 3.71 ± 1.55 |
| *tRNS-Noise* | 0 mA | 7.34 ± 1.47 | 0 mA | 4.87 ± 1.18 |
| *tRNS-Control* | 1.5 mA | 4.44 ± 1.54 | 0 mA | 1.48 ± 0.89 |

### *2.5.2 Adding noise centrally to the visual cortex with tRNS improves detection*

The tRNS-Noise experiment used the same visual detection task as the Visual-Noise experiment but instead of presenting noise visually on the screen, it was applied centrally to the visual cortex using tRNS with intensities of 0, 0.5, 0.75, 1 and 1.5 mA.

Two participants were excluded from the analysis because one performed below chance level (subthreshold group) and one displayed a ceiling effect (suprathreshold group) in the zero noise condition. This left a total number of 36 participants in the analyses (20 in the subthreshold group).

To test how much current reached the brain, we used a simplified spherical model to simulate the electrical field distribution induced by different frequency components of our tRNS signal (see table 1). The induced electrical field strength varied from approximately 1, 1.6, 2, to 3 V/m (for intensities of 0.5, 0.75, 1 and 1.5 mA, respectively), thus confirming a near linear increase of the induced effect. Note that unlike transcranial direct current stimulation (tDCS), tRNS does not produce tingling or other sensations for the intensities used here.

Applying tRNS to the visual cortex improved detection accuracy and this effect was significantly larger in the subthreshold stimuli group than in the suprathreshold stimuli group (Figure 2-4A, significant *Group* main effect tested with a repeated measures ANOVA, F(1,34) = 7.589, $p = 0.009$). Plotting detection accuracy as a function of tRNS intensity revealed the typical inverted U-shape relationship that was observed for the detection of subthreshold stimuli in individual subjects (Figure 2-1C, middle panel, orange) and at the group level (Figure

2-4A, orange). In contrast, tRNS had very little effect when administered during the detection of supra-threshold stimuli (Figure 2-1C, middle panel & Figure 2-4A, blue). The difference between subthreshold and suprathreshold groups was most pronounced for the 0.5 mA and 1 mA intensities, however, significance was only reached at uncorrected levels ($t(18) \geq 2.357$, $p \leq 0.030$ pre-planned comparisons, corrected alpha level = 0.0125).

The distribution of the individual optimal noise levels (Figure 2-4B) peaked at a tRNS intensity of 1mA for the subthreshold stimuli group, while it was nearly evenly distributed across all noise conditions in the suprathreshold stimuli group. For the latter group, this suggests that the optimal noise level varied in a close to random manner across subjects. The maximum improvement in accuracy caused by tRNS was significantly greater in the subthreshold stimuli group (13.6%) compared to the suprathreshold stimuli group (7%, $t(28.243) = 2.281$, $p = 0.030$; Cohen's d=0.81, Figure 2-4C). This was again confirmed by our additional analysis that determined the optimal noise level and the associated detection improvement in an independent manner (subthreshold: 11.1% accuracy improvement, suprathreshold: 4.8% accuracy improvement; $t(26.457) = 2.397$, $p = 0.024$; Cohen's d=0.77). Similar to the results obtained in the Visual-Noise experiment, we found a significant correlation ($r(34) = -0.52$, $p = 0.001$) between detection accuracy for zero noise trials and the maximum improvement observed for optimal tRNS intensities (Figure 2-4D). Two participant in the suprathreshold group reached 100% accuracy when noise was added with tRNS to the visual cortex. The maximum improvement of these participants (both 12.5%) exceeded the group mean of 7.3%. In summary, adding tRNS to the visual cortex induced a pattern of behavioural results highly similar to adding visual noise on the screen, suggesting that the SR phenomenon can be observed when electrical noise is added directly to cortical circuits of human participants engaged in a visual detection task.

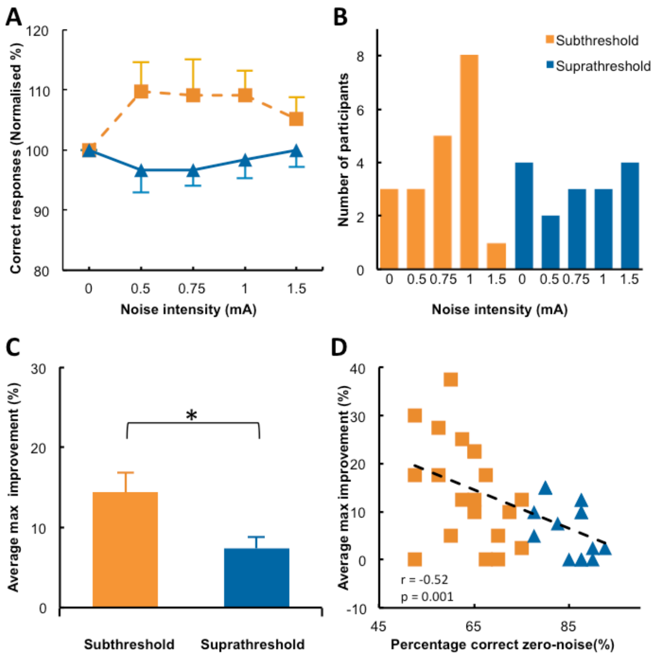

*Figure 2-4 Results when noise is added centrally to the visual cortex.*
**A)** Detection accuracy relative to the zero noise condition is shown for each noise level in the subthreshold and suprathreshold stimulus groups. **B)** Distribution of the individual optimal noise levels. **C)** The average maximum improvement was significantly different between the subthreshold and suprathreshold groups (* $p < 0.05$). **D)** A significant correlation was present between baseline performance and maximal improvement, indicating that participants with low detection accuracy in the zero noise condition benefited most from adding optimal noise. Conventions are the same as in Figure 2-3.

### *2.5.3 Applying tRNS to other cortical areas does not influence detection*

One participant was excluded from the analysis in the subthreshold group because performance in the zero noise condition was below chance level. This left a total number of 19 participants in the analyses (9 in the subthreshold group).

Previous research has suggested that the retina and/or the optical nerve are highly susceptible to alternating currents that can spread to the eyes via the skin, even if the stimulation electrodes are placed far away. Spreading currents that alternate with a frequency of 10-30 Hz are known to cause phosphenes (Schutter & Hortensius, 2010; Turi et al., 2013), which is a major confound for visual detection accuracy. Even though phosphenes are not evoked by alternating currents with frequencies > 100 Hz (Turi et al., 2013) as used in our study we performed a control experiment (tRNS-Control) to rule out the possibility that the improvement in detection accuracy was caused by current spreading to the retina and other unspecific tRNS effects. We used the identical protocol and stimulation parameters as in the tRNS-Noise experiment, except the electrodes were placed on the vertex and forehead. This set-up has been demonstrated to induce more intense phosphenes than the visual cortex- vertex montage used in experiment 2 (Schutter & Hortensius, 2010).

Applying tRNS over the vertex and forehead did not improve detection accuracy in either group, which exhibited a very similar pattern of results (Figure 2-5A, *Group* main effect and pre-planned comparisons all $p \geq 0.276$, see also Figure 2-1C (third column). In contrast, a significant performance deterioration was found in the suprathreshold group for the 0.75 mA noise intensity but only at uncorrected levels ($t(9) = -2.685$, $p = 0.025$, corrected alpha level = 0.0125). This null-effect is in line with the distribution of individual optimal noise levels (Figure 2-5B), which does not show a clear peak. The maximum improvement was small for both groups (subthreshold: 5%; suprathreshold: 4.4%; Figure 2-5C). In the additional analysis we did not find a significant difference between sub- and suprathrehold groups either ($t(17) = .533$, $p = 0.601$) and effect sizes were generally small (table 2). The correlation between detection accuracy for zero noise trials and the maximum improvement observed for optimal tRNS intensities did not reach significance, indicating that the effects caused by tRNS to the frontal lobe did not depend on detection accuracy in the zero noise condition (Figure 2-5D). Finally, there was a significant difference between the maximum improvement in the subthreshold groups of the tRNS-Control experiment and tRNS-Noise experiments ($t(26) = 5.447$, $p = 0.028$), indicating that the addition of noise to the visual cortex significantly enhanced detection performance when compared to our control experiment.

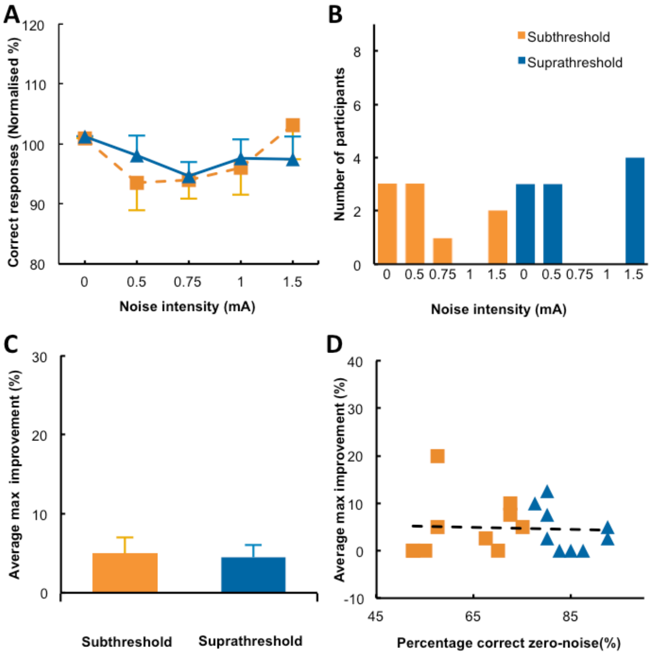

*Figure 2-5 Results of the tRNS control Experiment.*
**A)** Detection accuracy relative to the zero noise condition is shown for each noise level in the subthreshold and suprathreshold stimulus groups. **B)** Distribution of the individual optimal noise levels. **C)** The average maximum improvement was not significantly different between the subthreshold and suprathreshold groups. **D)** The correlation between baseline performance and maximal improvement was not significant. Conventions are the same as in Figure 2-3.

## 2.6 Discussion

This study provides direct evidence for enhanced detection of subthreshold visual stimuli when tRNS is added centrally to the visual cortex at an optimal intensity. When tRNS intensities were increased (ranging from 0 to 1.5 mA) the detection accuracy of subthreshold visual stimuli changed according to an inverted U-shape function, typical of the SR phenomenon. When the optimal level of noise was added to the visual cortex, detection performance improved significantly relative to the zero noise condition. It also improved to a similar extent when noise was added to the visual stimuli. The noise enhancing effect was not observed for suprathreshold stimuli.

Optimal noise intensities varied substantially across individuals, a finding that is well known when noise is added to the stimulus directly (Collins et al., 1996; Martinez et al., 2007). We accommodated this variability by determining the optimal noise intensities at the individual level rather than at group level. A split-half analysis was used to minimizes the risk of statistical "double-dipping". This analysis confirmed that both optimal visual noise and optimal tRNS noise had a signal-enhancing effect for subthreshold but not suprathreshold stimuli, an important characteristic of the SR phenomenon. Additionally, when intensities were weaker or stronger than optimal, there was little to no effect on detection accuracy. When plotted, these results show an inverted U-shaped tuning curve, a hallmark feature of the SR phenomenon (Moss, 2004). It is worth noting that SR-effects induced with tRNS were qualitatively similar to those observed when noise was added to the visual stimulus, even though the effect magnitude was somewhat larger in the Visual-Noise than the tRNS-Noise experiment. Thus, our results suggest that online tRNS adds noise to neural processing that has a similar effect as adding noise to the visual stimulus.

In order to determine whether tRNS induced electrical noise in the cortex, we used simulations based on a spherical head model. Simulation results suggested that the induced electrical field ranges from approximately 1 to 3 V/m (scaling quasi-linearly with tRNS intensity), and that all stimulation frequencies were transmitted to the cortex. Note that the estimated field strength is too small to directly depolarize cortical neurons or to cause conscious sensations (e.g. tingling of the skin) in the participants however it is sufficiently strong to modulate cortical processing after continuous application (Fertonani et al., 2011; Terney et al., 2008). It is known that the effect of tCS also depends on the morphology of the stimulated neuronal tissue (Radman, Ramos, Brumberg, & Bikson, 2009). Because of the complex morphology of the visual cortex we cannot exclude the possibility that different retinotopic coordinates received different levels of stimulation. In the design of our experiment we attempted to reduce the potential for bias by presenting the stimulus 5 times at each of the 8 locations in each experimental run. Moreover, a post-hoc control analysis testing whether the tRNS effect differed for targets in the left versus right and lower versus upper visual hemifields did not reveal systematic modulation.

The effects we observed are likely to reflect the acute/online influence of tRNS rather than after-effects that accumulate over time since stimulation was only applied for short intervals (2.04sec) and followed by long periods of no stimulation. Furthermore, Pirulli et al. (2013) reported that tRNS only influenced behavioural performance when applied during (online) a perceptual learning task, and not when it was applied prior to task learning (offline). They hypothesised that tRNS could induce temporal summation of small depolarizing currents that interact with the ongoing activity of cortical neurons. The order of tRNS blocks was also randomized over participants to prevent any order or intensity dependent after-effects. We also eliminated the possibility that results may be due to a general increase in arousal, tRNS induced phosphenes or other unspecific effects through our tRNS-Control experiment. Detection accuracy did not improve when a control electrode montage was used. The sample size in the tRNS-Control experiment was smaller than the sample size in the tRNS-Noise experiment. However, a power analysis considering the experimentally determined effect size of 0.26 for the tRNS-Control experiment and a power of 0.6 (table 2, power of the control analysis of the tRNS-Noise experiment) revealed that 344 participants would be needed to reach a significant effect for alpha=0.05. This suggests that the lack of a significant effect in the tRNS-Control experiment does not primarily result from the smaller sample size but rather from the low efficacy of the control stimulation.

Our study provides behavioural evidence for a SR mechanism when tRNS is added to neural networks in human cortex. This suggests that not only single neurons, but also cortical networks processing visual stimuli exhibit non-linear system properties, extending pervious work showing SR-effects at the neural network level in vitro (Manjarrez et al., 2007; Swain & Longtin, 2006). Our findings are also consistent with previous studies that demonstrate SR based detection enhancement even though the to-be-detected stimulus and the noise were presented to different modalities or effectors (Kitajo et al., 2003b; Lugo et al., 2008; Manjarrez et al., 2007). Note, however, that when both noise and stimuli are presented to a receptor one cannot exclude that SR-effects emerge subcortically, e.g. in the superior colliculus, a well-known multisensory integration area. Given what is known about the spread of non-invasive brain stimulation within cortex, it is highly unlikely that tRNS currents were sufficiently strong to modulate subcortical structures. Therefore our results suggest that neuronal populations in cortex can benefit from the direct application of noise.

Our finding also lends indirect support to the hypothesis that non-invasive brain stimulation techniques in general might modulate brain function via a SR mechanism, but that the effect depends on the level of noise and brain activity (C. Miniussi et al., 2013). This proposal was first tested by applying TMS pulses with an intensity determined via the phosphene threshold to visual cortex and measuring its influence on detection accuracy. However, findings differed across studies and could not be unequivocally interpreted, partly because it is not clear whether the TMS pulses added noise to neural processing (Schwarzkopf et al., 2011) or suppressed task related activity (Harris, Clifford, & Miniussi, 2008). Others have shown that also cathodal tDCS can enhance the perception of difficult to detect stimuli (i.e. obliquely oriented gratings of higher spatial frequencies) when compared to easier to detect stimuli (Richards et al., 2015). The authors suggested that tDCS exerted its influence on visual perception by modulating the signal-to-noise ratio of neurons in visual cortex and speculated that this effect has been mediated by a SR mechanism. Even though our data cannot directly speak to TMS or tDCS experiments, our results are in support of the idea that neural processing at the network level exhibits non-linear system properties that are sensitive to the SR phenomenon, which can be quantified via behavioural readouts (see also Fertonani and Miniussi, 2016). A major advantage of tRNS is that the signal has well-defined noise characteristics and can be applied continuously during the task without depolarizing neurons.

### *2.6.1 Interpretational issues*

One limitation of our study is that despite the clear behavioural evidence we did not directly measure neural signals and how they might have changed by adding tRNS to the scalp. Based on previous studies that used an identical electrode placement and our modelling we hypothesized that the induced currents reached mainly visual cortex (Neuling et al., 2012). However, drawing firm conclusions which neural areas or processes have been influenced will require the use of neuroimaging methods (preferably electroencephalography) *during* tRNS application.

## 2.7 Conclusion

In summary, our results highlight the potential to exploit SR mechanisms via tRNS to modulate human behaviour via non-invasive brain stimulation. Even though we used visual perception as a model system, tRNS can be applied to all cortical areas indicating that SR-effects can be utilised for all functions that depend on non-linear cortical dynamics.

## 2.8 Supplementary Information

In addition to the group level analysis we show here for each experiment individual data.

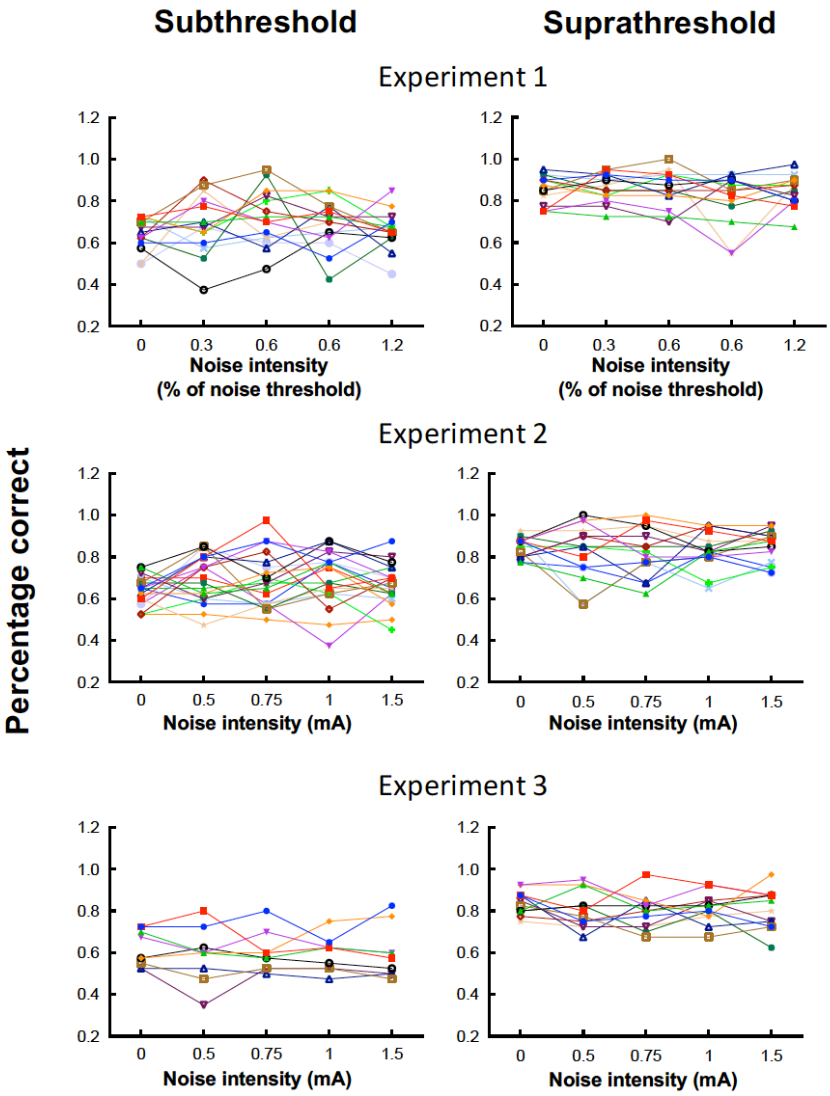

*Figure 2-6 S1 Individual detection data.*
In each figure the detection performance for each individual participant is shown for each experiment separately. The different colours represent individual participants.

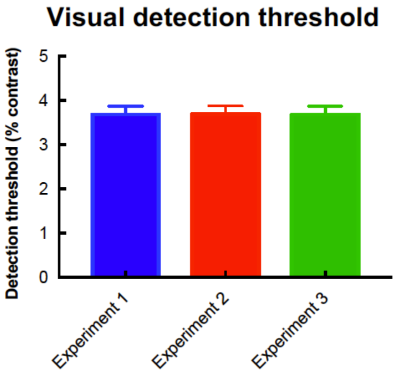

*Figure 2-7 S2 Visual detection thresholds.*
Each bar shows the detection threshold for each experiment in percentage contrast. Error bars indicate standard error of the mean.

# Chapter 3: Making up your mind: Enhanced Perceptual Decision-Making Induced by Stochastic Resonance During Non-Invasive Brain Stimulation

## 3.1 Abstract

Perceptual decision-making relies on the gradual accumulation of noisy sensory evidence until a specified boundary is reached and an appropriate response is made. It might be assumed that adding noise to a stimulus, or to the neural systems involved in its processing, would interfere with the decision process. But it has been suggested that adding an optimal amount of noise can, under appropriate conditions, enhance the quality of subthreshold signals in nonlinear systems, a phenomenon known as *stochastic resonance*. Here we asked whether perceptual decisions obey these stochastic resonance principles by adding noise directly to the visual cortex using transcranial random noise stimulation (tRNS) while participants judged the direction of motion in foveally presented random-dot motion arrays. Consistent with the stochastic resonance account, we found that adding tRNS bilaterally to visual cortex enhanced decision-making when stimuli were just below, but not well below or above, perceptual threshold. We modelled the data under a drift diffusion framework to isolate the specific components of the multi-stage decision process that were influenced by the addition of neural noise. This modelling showed that tRNS increased drift rate, which indexes the rate of evidence accumulation, but had no effect on bound separation or non-decision time. These results were specific to bilateral stimulation of visual cortex; control experiments involving unilateral stimulation of left and right visual areas showed no influence of random noise stimulation. Our study is the first to provide causal evidence that perceptual decision-making is susceptible to a stochastic resonance effect induced by tRNS, and that this effect arises from selective enhancement of the rate of evidence accumulation for sub-threshold sensory events.

Author contributions:

*Onno van der Groen:* Experimental design, Data collection, Data analysis and interpretation, Drafting of the manuscript
*Prof. Nicole Wenderoth:* Experimental design, Provided revisions to the manuscript
*Prof. Jason Mattingley:* Experimental design, Provided revisions to the manuscript
*Dr. Matthew Tang:* Experimental design, Provided revisions to the manuscript

***Under review:*** van der Groen, Onno, Matthew Tang, Nicole Wenderoth, and Jason Mattingley. 2017. 'Making up your mind: Enhanced perceptual decision-making induced by stochastic resonance during non-invasive brain stimulation', *bioRxiv*.

## 3.2 Results and Discussion

Noise is an intrinsic property of all biological systems (Tsimring, 2014). Typically, noise is viewed as being detrimental for neuronal computations and the behaviours they regulate (Faisal et al., 2008; Tsimring, 2014), including decision-making (Heekeren, Marrett, Bandettini, & Ungerleider, 2004). A key limiting factor in decision-making arises from noisy representations of sensory evidence in the brain (Brunton, Botvinick, & Brody, 2013; Kaufman & Churchland, 2013). On this view, noisy sensory information representations are not optimal, and this leads to errors in decisions. However, small amounts of noise added to a nonlinear system can increase the stimulus quality by increasing the signal-to-noise ratio (SNR)(Luca Gammaitoni, Hänggi, Jung, & Marchesoni, 1998). This phenomenon is known as *stochastic resonance*, and its expression has been demonstrated in different sensory modalities (Hanggi, 2002; Mark D McDonnell & Abbott, 2009; Moss, 2004). Stochastic resonance occurs when an optimal amount of noise is added to a sub-threshold signal, which makes the signal cross a decision threshold, and therefore enhances detection performance (Figure 3-1).

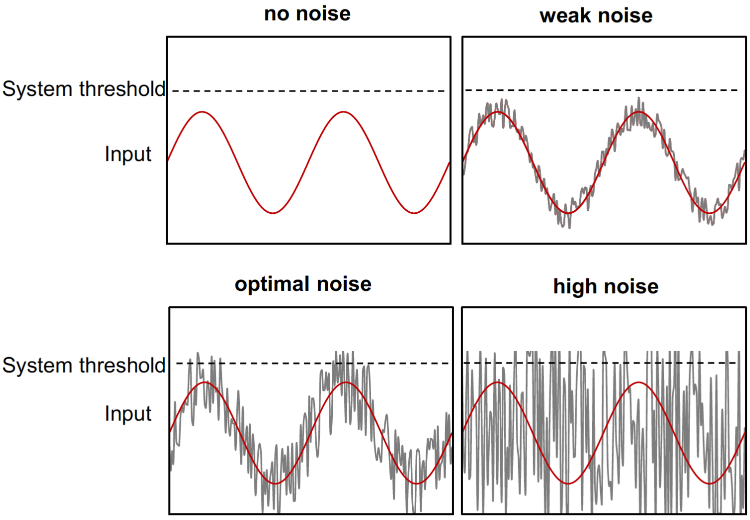

*Figure 3-1 Stochastic resonance effect.*
Stochastic resonance occurs when an optimal level of noise is added to a subthreshold signal. In this example the signal alone (red sinusoid) remains below the perceptual threshold (dotted line). Adding an optimal amount of noise raises the stimulus periodically above the system threshold. If the added noise is too weak the threshold is not crossed. Conversely, if the noise is too strong the signal remains buried and cannot be discriminated from the noise (Davis & Plaisted-Grant, 2015).

In a typical stochastic resonance experiment, predefined noise intensities are added to a signal. Adding too little noise does not cause threshold crossings when the signal is well below the detection threshold, and performance remains unaffected. By contrast, when too much noise is added the signal gets buried in the noise and performance declines (Collins et al., 1996; Lugo et al., 2008; Simonotto, Riani, Twitty, & Moss, 1997; Zeng et al., 2000). This results in an 'inverted U' relationship between noise intensity and detection performance, which is a key signature of the stochastic resonance effect (Hanggi, 2002; Mark D McDonnell & Abbott, 2009; Moss, 2004). At the neurophysiological level, it has been shown that adding an optimal amount of noise to a subthreshold signal pushes otherwise silent sensory neurons above the spiking threshold (Douglass, Wilkens, Pantazelou, & Moss, 1993; Hanggi, 2002; Kurt Wiesenfeld, David Pierson, Eleni Pantazelou, Chris Dames, & Frank Moss, 1994). A common way of adding noise in a stochastic resonance context is to add it directly to the sensory stimulus. In that case, the noise could increase peripheral receptor sensitivity (Mendez-Balbuena et al., 2012), which does not permit investigation of whether central neural processes in decision-making are sensitive to a stochastic resonance mechanism. Recently, we showed it is possible to induce a stochastic resonance effect in a simple detection task when noise is added to the cortex directly with tRNS (van der Groen & Wenderoth, 2016). In that study, participants had to detect a weak visual stimulus which was either sub- or suprathreshold. On each trial, tRNS with a predefined intensity was added to the visual cortex. We demonstrated that adding an optimal noise level with tRNS significantly enhanced detection performance for subthreshold, but not suprathreshold, stimuli.

Here we asked whether perceptual decision-making, as opposed to mere detection, can be enhanced for subthreshold visual stimuli by the application of tRNS over visual cortex, either bilaterally (Experiment 1) or unilaterally over the left and right visual cortex (Experiments 2 and 3). To examine these effects, we used drift diffusion modelling (DDM, see Figure 3-2A) (Roger Ratcliff, 1978; R. Ratcliff & McKoon, 2008) to uncover what aspects of the decision process were influenced by tRNS. Under the DDM framework, decision-making requires the collection of noisy sensory evidence over time. The collection of sensory evidence continues until a criterion is reached, and based on the collected sensory evidence, a decision is made (J. Braun & Mattia, 2010; Gold & Shadlen, 2007). The DDM is a highly successful approach that has been used over a wide range of tasks (Forstmann, Ratcliff, & Wagenmakers, 2016).

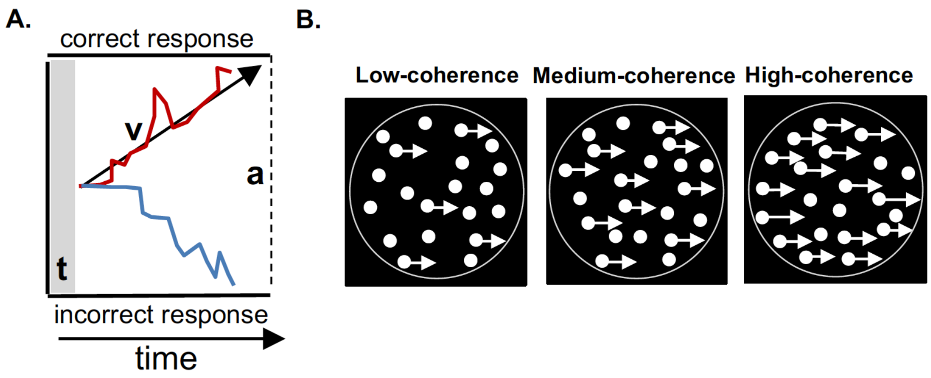

*Figure 3-2 Drift Diffusion framework.*
**A)** Schematic of the Drift Diffusion Modelling (DDM) framework used to model perceptual decision-making in the dot motion task. In the model, evidence is accumulated over time until a response boundary is crossed. t is the non-decision time, which includes the time taken to execute a motor response. v is the drift rate, which reflects the rate at which sensory evidence is accumulated and is taken as an index of the quality of sensory information. a represents the boundary separation, indicating how much information is needed to make a decision. **B)** Schematic of the random dot-motion task in which participants judged whether signal dots moved on average to the left or right. Task difficulty was titrated by altering the proportion of coherently moving dots amongst randomly moving dots. In this example the coherent motion is rightward, but in the experiment the dots were equally likely to move toward the left or right. For display purposes, we depicted here the outline of the imaginary circle in which the dots were presented.

We used a random-dot-motion task (RDM-task) as the perceptual decision-making task of choice (see Supplemental Information). The RDM-task is widely used in studies of perceptual decision-making, and has well characterized neural correlates (Ferrera, Rudolph, & Maunsell, 1994; Shadlen & Newsome, 2001). Participants fixated on a centrally presented array of randomly moving dots within which a proportion of the dots moved coherently in a common direction (leftward or rightward; see Figure 3-2B). Participants judged the common direction of movement (two-alternative forced-choice/2-AFC) as quickly and accurately as possible. The difficulty of the task was parametrically manipulated by altering the proportion of signal dots that moved coherently in a given trial (3%, 6%, 12%, 25% or 50% coherence). The benefit of this task is that it allows for the continuous accumulation of sensory evidence over a period of several hundred milliseconds, which facilitates investigation of the underlying processes involved in decision-making (Britten, Shadlen, Newsome, & Movshon, 1992; Gold & Shadlen, 2007; Newsome, Britten, & Movshon, 1989).

If the stochastic resonance model applies to perceptual decision-making, then the addition of relatively small amounts of noise should enhance motion discrimination performance. The added noise will likely increase the quality of the sensory evidence for coherent motion trials in which the signal is just below threshold, but not for trials in which the signal is well below or above threshold. Conversely, the addition of large amounts of noise should either have no effect on perceptual thresholds, or should impair performance slightly for displays at or above threshold (Moss, 2004). We therefore applied four different tRNS intensities (0.25, 0.375, 0.5 and 0.75 mA; 100-640 Hz zero-mean Gaussian white noise) while participants engaged in the RDM-task. These tRNS intensities result in current densities that we have shown previously are able to induce a stochastic resonance effect in a visual contrast detection task (van der Groen & Wenderoth, 2016). The tRNS was applied in blocks of 20 trials at one of the four intensities, with each block of stimulation followed by a 20-trial block of no-stimulation to minimise build-up of any cumulative effects of the stimulation. Participants were blinded to the tRNS conditions. Consistent with several previous investigations, no participant reported awareness of the stimulation during de-briefing (Ambrus, Paulus, & Antal, 2010; Fertonani et al., 2011) .

### *3.2.1 Experiment 1: Effect of bilateral visual cortex stimulation*

In Experiment 1, we stimulated visual cortex bilaterally with tRNS in 15 participants (see Figure 3-3 and Figure 3-7 S2). The coherence levels of 3% and 6% were subthreshold (average detection performance < 0.63%), i.e., performance was below the detection threshold, which corresponded to 75% correct in our task. For the analysis, we calculated the group %correct-choice-index (%CCI) for each coherence level and each tRNS intensity by dividing the %correct motion-direction responses under tRNS by the %correct responses when no tRNS was applied (baseline), as given in the following formula:

$$(\%\mathrm{CCI}) = \%\mathrm{Corr}(i)/\%\mathrm{Corr}(\mathrm{zero\ noise})$$

where *i* denotes each of the 4 tested noise intensities. As shown in the left panel in Figure 3-3, for the 6% coherence condition, which was just below threshold in the no-tRNS condition, motion discrimination performance improved when tRNS was applied at a relatively low intensity, whereas performance remained unaffected for the other coherence levels and noise intensities. To quantify these effects, we performed a 4 (tRNS intensity) x 5 (coherence level) within-subjects ANOVA on the %CCI data. There was a significant interaction between coherence level and tRNS-intensity ($F(12,156) = 2.47$ $p < 0.01$, Cohen's f= 0.43). To isolate the source of this interaction, one-way ANOVAs were conducted for each coherence level separately. For the 6% coherence condition only (red symbols in Figure 3-3), performance was significantly affected by the different tRNS intensities ($F(3,39) = 3.56$ $p = 0.02$ Cohen's f=0.52 ). There were no other significant main effects or interactions for the coherence conditions of

3%, 12%, 25% or 50%. Post-hoc tests were conducted to compare performance in the 6% coherence condition at each noise level against the baseline. All p-values were corrected for multiple comparisons. These comparisons revealed that a tRNS intensity of 0.25mA significantly enhanced motion discrimination performance relative to baseline ($t(13) = 3.39$ $p_{corrected} < 0.02$). A similar enhancement was evident for the 6% coherence level at an intensity of .375mA, but this effect did not survive our stringent correction for multiple comparisons, ($t(13) = 2.53$, $p_{corrected} > 0.1$).

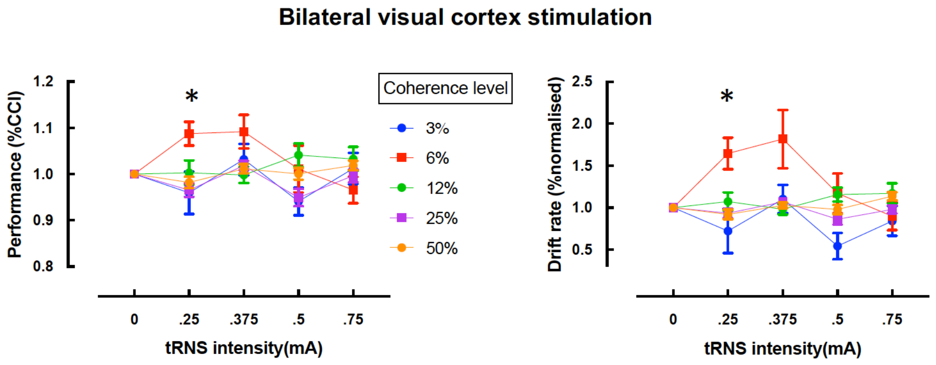

*Figure 3-3 Bilateral visual cortex stimulation results.*
*Effects of transcranial random noise stimulation (tRNS) on perceptual decision-making in the dot-motion discrimination task for bilateral stimulation. The left panel shows performance for each motion coherence level as a function of tRNS intensity. The right panel shows the drift rate derived from modelling of the data shown in the corresponding plot to the left.* $*p_{corrected} < 0.05$.

These results suggest that perceptual decision-making for sensory stimuli that are just below threshold can be improved by adding a small amount of neural noise over bilateral visual cortex, consistent with predictions arising from the stochastic resonance principle (Moss, 2004).

Next we employed the drift diffusion framework to accurately model the processes involved in decision-making based on the accuracy and response time data obtained from the decision-making task. Specifically, we used the hierarchical drift diffusion model (HDDM, (Wiecki, Sofer, & Frank, 2013)) to determine which aspect of decision-making was affected by tRNS. We normalized the obtained DDM-parameters relative to the zero noise condition in the same way as the behavioural data, as described above. As shown in the right panel of Figure 3-3, the drift rate was markedly affected by tRNS for the 6% coherence condition, whereas it appears to be unaffected for the remaining coherence levels. We submitted the drift-rate parameter to a 5 x 4 repeated measures ANOVA. This analysis revealed a significant main effect of tRNS-intensity ($F(3,39) = 2.85$, $p = 0.049$) and of coherence level ($F(4,52) = 3.18$, $p = 0.02$ on drift rate, as well as a significant tRNS-intensity x coherence level interaction ($F(12,156) = 3.22$, p

< .01, Cohen’s f = 0.47). To isolate the source of the significant interaction, one-way ANOVAs were conducted for each coherence level separately. Consistent with the behavioural data, there was a significant effect of tRNS intensity on drift rate in the 6% coherence condition (F(3,39) = 5.63, p < .01, Cohen’s f = .58), but no significant effects for the other coherence levels (3%, 12%, 25%, 50%).

Post-hoc tests were conducted to compare performance in the 6% coherence condition against the baseline for each noise level. For the tRNS intensity of .25mA, the drift rate for the 6% coherence condition was significantly higher than baseline (t(13) = 3.44, $p_{corrected} < 0.02$, corrected for multiple-comparisons). A similar benefit for the 6% coherence condition was apparent for the tRNS intensity of .375mA, but this effect did not survive correction for multiple comparisons (t(13) = 2.55, p = 0.1). Separate 5 x 4 repeated measures ANOVAs revealed no significant effects for the bound-separation parameter (all p > 0.06), and no significant effects for non-decision time (all p > 0.13).

Previous studies of visual motion discrimination have shown reliable effects of offline transcranial electrical stimulation – as opposed to the online effects reported here – following unilateral stimulation of left or right visual cortex in isolation (Antal, Varga, et al., 2004; Kar & Krekelberg, 2014; Zito et al., 2015). We therefore conducted two further experiments to determine whether the stochastic resonance effects we observed for bilateral tRNS in Experiment 1 also arise for unilateral visual stimulation. We also modelled the current spread for the electrode montage used in each experiment using the SimNibs toolbox (Thielscher, Antunes, & Saturnino, 2015) (Figure 3-4).

### *3.2.2 Experiments 2 and 3: Effect of unilateral visual cortex stimulation*

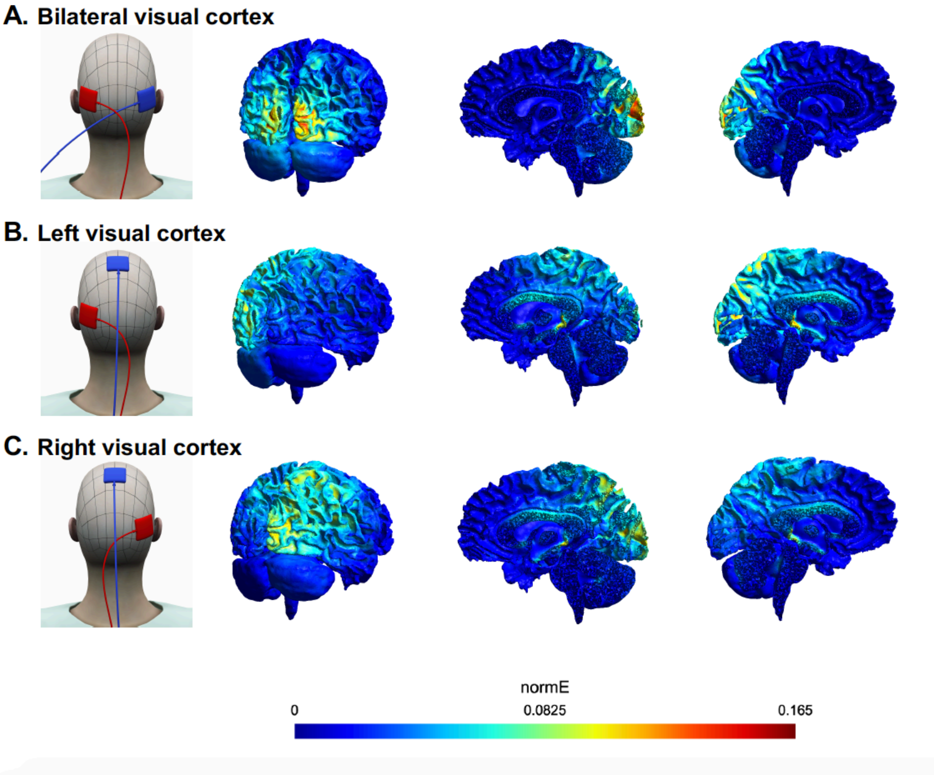

*Figure 3-4 Electrode montages and modelled electrical field strength for each of the three experiments.* **A.** Bilateral visual cortex stimulation (Experiment 1). **B.** Left visual cortex stimulation (Experiment 2). **C.** Right visual cortex stimulation (Experiment 3).

In experiments 2 and 3 we applied tRNS unilaterally to the left and right visual cortex, respectively, using two new groups of 15 participants each. Figures 3-5A and 3-5B show the behavioural results for these two experiments. Neither left nor right unilateral tRNS produced the characteristic inverted-U tuning curve observed in Experiment 1 for the 6% coherence condition during bilateral stimulation. To characterize the data statistically, we employed the same analytic approach as for the bilateral tRNS experiment, for both the behavioural data and the drift diffusion modelling. There was no significant interaction between stimulation intensity and coherence level for either left unilateral or right unilateral visual cortex stimulation ($p >$ .05 for all key comparisons). Thus, there was no evidence for the stochastic resonance effect observed during bilateral stimulation in experiment 1.

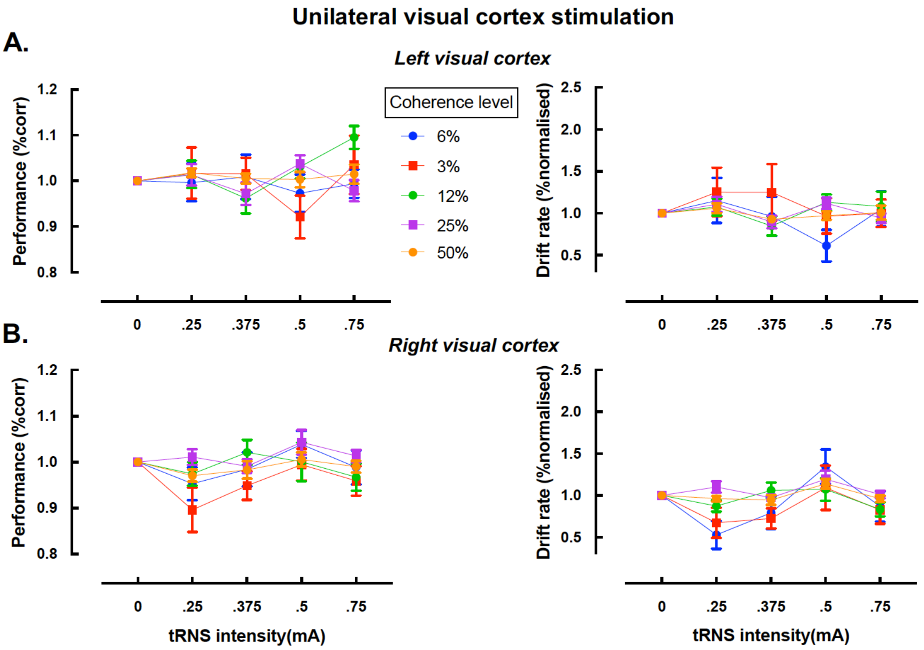

*Figure 3-5 Results unilateral visual cortex stimulation.*
Effects of transcranial random noise stimulation (tRNS) on perceptual decision-making in the dot-motion discrimination task for unilateral stimulation for the left visual cortex **(A)** and right visual cortex **(B)** stimulation. The left panels show performance for each motion coherence level as a function of tRNS intensity. The right panels show the drift rate derived from modelling of the data shown in the corresponding plots to the left.

Analysis of the baseline data in all three experiments revealed no interaction between coherence level and tRNS intensity (repeated measures ANOVA with within-subjects factor of coherence level and between-subjects factor of experiment, F(2,39) = 1.15, p > .32), suggesting that the stochastic resonance-effect observed in Experiment 1 was not driven by differences in baseline performance between the three experiments. Across all three experiments, there was a highly significant main effect of coherence level on performance, as expected. For completeness, we also report here a small number of significant main effects which are not related to the central stochastic resonance hypothesis under examination in this study (see also Figure 3-7 S2). First, there was a small but consistent main effect of tRNS intensity on accuracy during right visual cortex stimulation, F(3,39) = 3.13 p = .036, Cohen's f =0.49. Post-hoc contrasts revealed that this effect was driven by overall poorer performance for the .25mA tRNS intensity, regardless of motion coherence level, t(69) = -2.78 $p_{\text{corrected}} < 0.03$. This decrease in performance was mirrored by a significant main effect of tRNS-intensity on drift rate (see Figure 3-5B and Table 3-1 S1), (F(3,39) = 4.54 p < .01, Cohen's f = 0.59, which was again specific to the .25mA tRNS intensity, (t(69) = 2.67 $p_{\text{corrected}} = .04$), regardless of motion coherence level. Second, there was a significant main effect of coherence level on bound-separation during stimulation of the right visual cortex, F(4,52) = 3.09 p = .024, Cohen's f =

0.4 (see Supplemental Information). Post-hoc tests showed that the bounds were significantly closer together for the highest (50%) coherence condition, $t(55) = 3.16$ $p_{corrected} < .04$, relative to baseline), but there were no significant effects on bound separation for the other coherence levels.

## 3.3 Conclusion

We have shown that adding a small amount of noise bilaterally to the visual cortex can enhance perceptual decision-making in a motion discrimination task, particularly for subthreshold stimuli (6% coherence). When modelled as a drift-diffusion process, this tRNS-induced performance improvement coincided with an increase in the rate of evidence accumulation, reflected as a change in the model's drift-rate parameter. The same model revealed no change in either bound-separation or non-decision time, suggesting that an optimal level of neural noise exclusively improves perceptual decision-making by enhancing sensory information quality, consistent with a stochastic resonance mechanism ((Hanggi, 2002; Mark D McDonnell & Abbott, 2009; Moss, 2004), see Supplemental Information for the model fits). In line with previous work (van der Groen & Wenderoth, 2016), we showed that the stochastic resonance effect was strongest when appropriate tRNS intensities were added to the 6% coherence condition, i.e. to a *subthreshold* stimulus, as indicated by the average baseline detection accuracy of 60%. Note that all tRNS intensities and coherence levels were randomized over participants to account for any aftereffects, fatigue or learning effects across conditions.

There was no evidence for a stochastic resonance effect when noise was applied unilaterally to the visual cortex. This absence of a performance-enhancing effect for unilateral tRNS was not due to differences in baseline performance between the groups: detection performance in the 6% coherence condition was similar across experiments (Experiment 1 – 60%; Experiment 2 – 58%; Experiment 3 – 57%). Modelling of the electrical field for each electrode montage (Figure 3-4) indicated a higher peak current when the tRNS was applied bilaterally than in the unilateral stimulation conditions. It is unlikely that this apparent difference in current densities prevented a stochastic resonance effect for the unilateral stimulation conditions, however, because the same absolute current densities during bilateral stimulation were also reached during unilateral stimulation but at higher tRNS intensities.

The visual stimuli employed in our motion discrimination task were always presented in the centre of the display, and thus would have been processed initially by visual areas in both the left and right hemispheres (d'Avossa et al., 2007). Given that unilateral visual cortex stimulation did not influence motion-discrimination performance, it is most parsimonious to conclude that visual areas in *both* hemispheres must be stimulated concurrently with tRNS for the stochastic resonance effect to occur. Because of the relatively diffuse nature of transcranial electrical stimulation in general (Woods et al., 2016), it is not possible to determine the specific anatomical regions that mediate the stochastic resonance effect we observed. The primary visual cortex (V1) (Ajina, Kennard, Rees, & Bridge, 2015) and motion area V5/MT are both crucial for the processing of dynamically moving visual stimuli (Newsome & Pare, 1988; Salzman, Murasugi, Britten, & Newsome, 1992; Thakral & Slotnick, 2011). These two areas are highly interconnected, so our bilateral stimulation protocol might have impacted motion processing in area V5/MT, enhanced signal quality in area V1, or both. Further work using more focal stimulation techniques (e.g., transcranial magnetic stimulation) will be needed to pinpoint the visual areas responsible for the stochastic resonance effects we report here.

Our results are in line with recent work that employed a similar task to show that decision-making is sensitive to the addition of noise to visual motion stimuli (Trevino, De la Torre-Valdovinos, & Manjarrez, 2016). Critically, our findings extend these results by demonstrating that a stochastic resonance effect can be induced in a decision-making task when noise is directly applied to the visual cortex with tRNS (C. Miniussi et al., 2013; Schwarzkopf et al., 2011). Moreover, we are the first to show that this stochastic resonance effect enhances the quality of information processing as indicated by an accelerated rate of evidence accumulation. The underlying mechanism for the observed tRNS effect is not completely understood. However, single unit recordings have shown that sensory neurons in the visual cortex are sensitive to a stochastic resonance mechanism, e.g., there is an increase in the SNR of the firing rate of neurons when an optimal level of noise is applied to a visual stimulus (Funke et al., 2007). This is likely due to the recruitment of voltage-gated sodium channels by the noise (Bromm, 1968; Onorato et al., 2016; Schoen & Fromherz, 2008).

## 3.4 Supplementary Information

### *3.4.1 Supplemental figures*

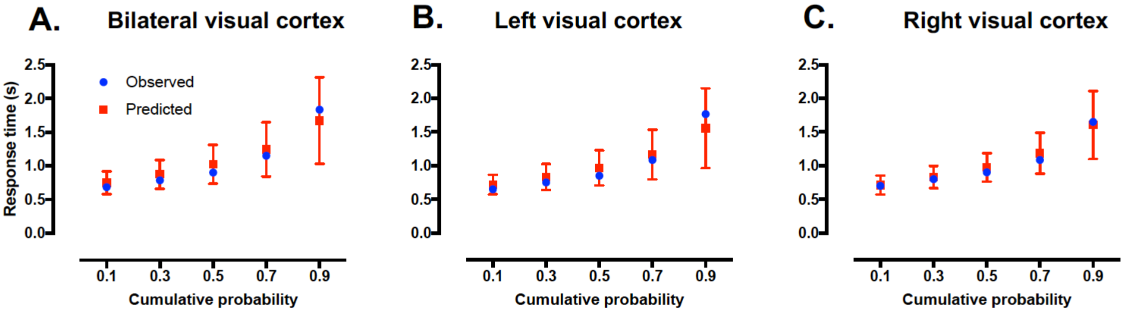

*Figure 3-6 S1 Quantile probability plots of mean response times in the motion discrimination task. Quantile probabilities are plotted separately for the three stimulation conditions in Experiments 1, 2 and 3.* Figure A shows the data for the bilateral stimulation. Figure B shows the data for left unilateral and Figure C for right unilateral stimulation. Observed response times for five quantiles (10, 30, 50, 70 and 90%) are shown in blue, plotted as a function of their cumulative probability. Red symbols show predicted quantile means, with error bars indicating the standard deviation of the posterior predictive distribution of the model. The plots show that the hierarchical drift diffusion model provides a good fit to the data, and that the mean response times are comparable across the experiments.

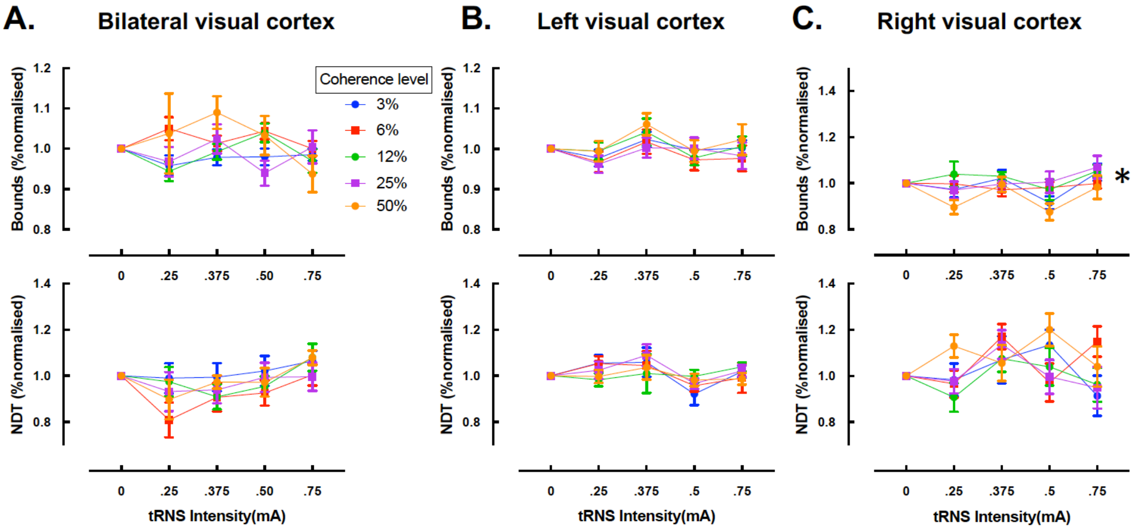

*Figure 3-7 S2 The HDDM results for the bounds and non-decision-times for the different experiments.* Figure A shows the data for the bilateral stimulation. Figure B shows the data for left unilateral and Figure C for right unilateral stimulation. In the right unilateral stimulation condition (B) we found a significant main effect of coherence level on bound-separation F(4,52) = 3.088, p = 0.024, Cohen's f: 0.4. Post-hoc tests showed that the bounds were significantly closer together for the highest (50%) coherence condition, t(55) = -3.157, p < .01.

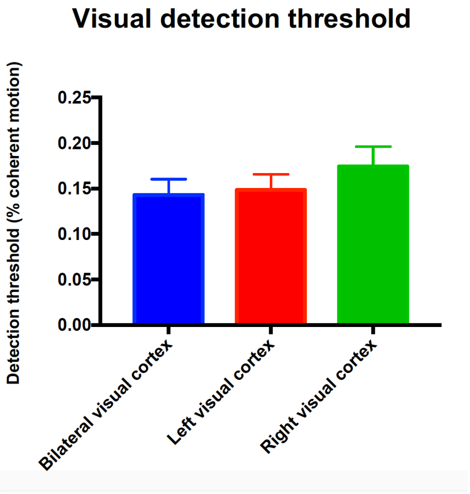

*Figure 3-8 S3 Visual detection thresholds.*
Each bar shows the detection threshold for each experiment without tRNS stimulation in percentage coherent motion. Error bars indicate standard error of the mean.

In addition to the group level analysis we show here for each experiment the detection thresholds.

In figure 3-9 S4, the individual data for the 6% coherence condition is shown since this is the only condition where we found a significant effect of tRNS.

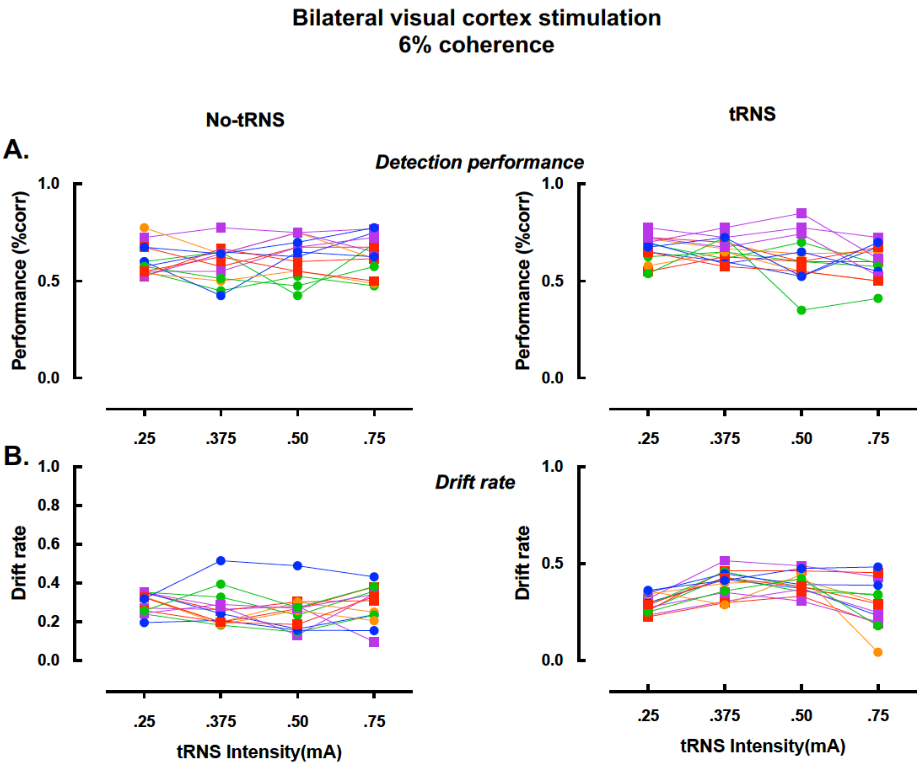

*Figure 3-9 S4 Individual data.*
Figure A shows the non-normalised individual detection performance and figure B shows the non-normalized drift rate. Only the individual data for the 6% coherence condition is shown since this is the only coherence condition where we found a significant effect.

### *3.4.2 Supplemental table*

*Table 3-1 S1 Modelled electrical field strengths for different transcranial electrical current stimulation intensities and frequencies.*
The modelling shows that all stimulation frequencies were transmitted to the brain, and that the current applied was of sufficient intensity to reach the cortex (V/m).

| | **Bilateral stimulation** | | | | **Unilateral stimulation** | | | |
|---|---|---|---|---|---|---|---|---|
| **Frequency (Hz)** | *.25mA* | *.375mA* | *.5mA* | *.75mA* | *.25mA* | *.375mA* | *.5mA* | *.75mA* |
| *100* | .85 | 1.25 | 1.63 | 2.6 | .85 | 1.25 | 1.63 | 2.6 |
| *150* | .85 | 1.25 | 1.63 | 2.5 | .85 | 1.25 | 1.63 | 2.5 |
| *200* | .85 | 1.25 | 1.62 | 2.5 | .84 | 1.25 | 1.62 | 2.5 |
| *250* | .84 | 1.24 | 1.62 | 2.5 | .84 | 1.24 | 1.62 | 2.5 |
| *300* | .84 | 1.24 | 1.62 | 2.5 | .84 | 1.24 | 1.62 | 2.5 |
| *350* | .84 | 1.24 | 1.62 | 2.5 | .84 | 1.24 | 1.62 | 2.5 |
| *400* | .84 | 1.23 | 1.62 | 2.5 | .83 | 1.23 | 1.62 | 2.5 |
| *450* | .84 | 1.23 | 1.62 | 2.5 | .83 | 1.23 | 1.62 | 2.5 |
| *500* | .84 | 1.23 | 1.62 | 2.5 | .83 | 1.23 | 1.62 | 2.5 |

## 3.5 Supplemental methods

### *3.5.1 Participants*

A total of 45 healthy adults participated in the study (15 in each experiment, 28 males, aged: 18 – 27 years, mean age = 22.5 years). All participants had normal or corrected-to-normal vision, and met the inclusion criteria for tRNS as assessed by a checklist prior to the experiment (Fertonani et al., 2015). Written informed consent was obtained for all participants. The study was approved by The University of Queensland Human Research Ethics Committee and was in accordance with the Declaration of Helsinki.

### *3.4.5 Transcranial random noise stimulation (tRNS)*

Each participant received four tRNS noise intensities twice (.25mA, .375mA, .5mA and .75mA; all delivered at frequencies between 100 and 640 Hz). Noise intensity order was randomized across participants. The tRNS was applied with a 0mA offset, and was applied for 20 trials followed by 20 trials of no-stimulation. This order was counterbalanced across participants. The tRNS was delivered via a battery-driven electrical stimulator (version DC-Stimulator PLUS, neuro-Conn). The maximum current density was 46.87 μA/cm$^2$, which is well within published safety limits (Fertonani et al., 2015). Electroconductive gel was applied to the contact side of the electrode (4 x 4 cm) to reduce skin impedance. In Experiment 1, the visual cortex was stimulated bilaterally, with electrodes placed 3.5 cm above the inion and 6.5 cm left and right of the midline in the sagittal plane. These coordinates were selected based on previous brain imaging and stimulation studies that investigated the offline aftereffects of transcranial current stimulation (tCS) on a motion detection task (Antal, Nitsche, et al., 2004; J. Hotson, Braun, Herzberg, & Boman, 1994; J. R. Hotson & Anand, 1999; Stewart, Battelli, Walsh, & Cowey, 1999; Walsh, Ellison, Battelli, & Cowey, 1998; J. D. G. Watson et al., 1993). In Experiment 2, the stimulation electrode was placed over the left visual cortex (positioned as described for Experiment 1), and the reference electrode was placed over the vertex (Cz in the 10-20 EEG-system). In Experiment 3, the stimulation electrode was placed at the homologous location over the right visual cortex, and the reference electrode was placed at the vertex as in Experiment 2.

### *3.5.2 Visual decision-making task*

All experiments took place in a dark and quiet room. Visual stimuli were generated using Matlab 8.0 (2012b) and the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997), and were presented using a Dell PC (T3400) running Windows XP with a NVIDIA Quadro FX 1700 graphics card. Stimuli were presented on an Asus VG428QE colour monitor with a resolution of 1920x1080 pixels, with a refresh rate of 60 Hz. The luminance of the monitor was gamma-corrected with a maximum intensity of 316.5 cd/m$^2$ and minimum of 0.33 cd/m$^{2.}$ Viewing distance was maintained at 62 cm using a chinrest, meaning the display subtended 46° x 27° (1.5' per pixel). We employed a two-alternative, forced-choice random-dot motion discrimination task (Newsome & Pare, 1988; Tang, Dickinson, Visser, & Badcock, 2015) in which participants judged the direction (leftward or rightward) of the coherently moving dots as quickly and as accurately as possible. Each block of 20 trials began with the presentation of a central fixation cross presented for 2000 ms. On each trial, a fixation cross was presented for 200 ms. The motion stimulus then appeared, and consisted of 100 square dots (3 x 3') within an aperture (radius 4.1°) at the centre of the screen. The dots were randomly positioned within the aperture on the first frame before rigidly translating at 1.5 deg/sec. If a dot was going to move outside the aperture on the next frame, it was wrapped to the opposite side of the aperture. The dot-motion display remained visible until response, up to a maximum duration of 3 s. Participants indicated their choices by pressing the left or right 'shift' key on a standard keyboard with the left or right index finger, respectively. If the participants did not respond within 3 s, the motion stimulus was extinguished, and the trial was counted as incorrect and excluded from further analysis. Participants were provided with immediate auditory feedback. A low-pitched tone indicated a correct response, a high-pitched tone an incorrect response, and a prolonged, low-pitched tone indicated a response that was too slow (i.e., > 3 s). A new trial commenced 2 s after the previous response.

A method of constant stimuli was used to determine global motion sensitivity. A proportion of the dots moved coherently to the left or right, and the remaining dots moved in random directions. Thus, for example, a coherence level of 3% indicates a display in which 3% of the dots translated coherently (left or right, depending on the trial), while the remaining 97% of dots moved in random directions. Five logarithmically spaced coherence levels (3%, 6%, 12%, 25% and 50%) were chosen, consistent with previous work (Curran & Lynn, 2009). The dots had a limited lifetime of 5 frames. In keeping with a common convention (e.g., Edwards and Badcock, 1993), half of the dots were black and half of the dots were white, all of which were presented on a mid-grey background.

To measure the effects of tRNS on visual motion discrimination, participants performed 10 blocks of 200 trials each, with different tRNS intensities. The first and the last blocks contained no tRNS. The four tRNS levels (.25mA, .375mA, .5mA and .75mA) were applied twice each in blocks 2 – 9, in random order. The first block served as practice, and the data obtained were not included in the analyses. Each block contained 200 motion discrimination trials, with an equal number of presentations of each motion coherence level, presented in a pseudo-randomized order (the total length of each block was ~ 6 mins). To minimize any build-up of tRNS effects, stimulation was applied for 20 trials before being turned off for the next 20 trials within each block. Coherence levels for stimulator-on and stimulator-off trials were balanced for each observer, and were combined during data analysis. Including electrode setup and data collection, the entire experiment took around 90 minutes per participant.

## 3.6 Data analysis

The same statistical procedures were used in all three experiments. In each experiment, one participant was excluded (3 in total) because the individual did not reach 80% correct responses in the highest coherence condition. The $\alpha$ level was set to 0.05 for all tests, adjusting for multiple comparisons using the Bonferroni correction. We used the same procedure to quantify the stochastic resonance effect as in our previous paper (van der Groen & Wenderoth, 2016). By normalizing the data to the mean of the noise-free trials, which were interspersed with active tRNS trials throughout the experiment, we were able to rule out any contribution from practice, learning or fatigue. The normalized behavioural data were subjected to a repeated-measures ANOVA with the factors of coherence level (5 levels: 3%, 6%, 12%, 25% and 50%) and tRNS-intensity (4 levels: .25mA, .375mA, .5mA and .75mA).

## 3.7 Modelling

### *3.7.1 Hierarchical Bayesian Drift Diffusion Modelling.*

Drift diffusion modelling (DDM) has been employed widely to disentangle the different component processes involved in simple decision-making tasks (R. Ratcliff & McKoon, 2008; R. Ratcliff & Smith, 2004). It captures three distinct stages of the decision process: (i) boundary separation, which indicates how much evidence must be accumulated before a response is made; (ii) information accumulation rate ('drift rate'), which is a measure of how rapidly evidence is accumulated. This depends on the quality of evidence in the stimulus, such that easier decisions result in a higher drift rate; and (iii) non-decision time, which is the time required to encode the stimulus and execute an appropriate motor response (R. Ratcliff & McKoon, 2008). We used the hierarchical drift diffusion model (HDDM) to fit the DDM parameters to the data (Wiecki et al., 2013). The HDDM uses a Bayesian method for estimating the DDM parameters, which allows simultaneous estimation of group and subject parameters. A benefit of the HDDM is that it outperforms other approaches when a small number of trials is available (R. Ratcliff & Childers, 2015).

We took a similar approach in our implementation of the HDDM as Herz and colleagues (Herz, Zavala, Bogacz, & Brown, 2016). We fixed the starting parameter, $z$ (also known as the bias parameter), to 0.5, which is chance level in a 2-AFC task. We modelled the data with the drift rate, bound separation and non-decision time as free parameters. We obtained parameter estimates for the conditions noise-on/noise-off, coherence level and tRNS intensity. We normalized the obtained parameters to the zero-noise (no tRNS) trials. This normalization procedure was the same as for the correct choice index (CCI) data. Markov chain Monte Carlo sampling methods were used for accurate Bayesian approximation of the posterior distribution of parameters (generating 20,000 samples, discarding 10,000 samples as burn-in and keeping every fifth subsequent sample). We visually inspected all traces of model parameters, their autocorrelation and computed the R-hat (Gelman-Rubin) convergence statistics to ensure that the models had properly converged (Wiecki et al., 2013). All R-hat values were below 1.1, verifying that convergence had been achieved (Brooks & Gelman, 1998). For each experiment, we plotted observed and predicted RTs for the 10, 30, 50, 70 and 90 percentile of trials (i.e., for the fastest 10% of trials, fastest 30% of trials, etc.) against the cumulative probability (see Figure 3-6 S1). These results indicate that the HDDM provided a good prediction of the observed data. The parameter estimates for bound separation and non-decision time (NDT) are shown in Supplemental Figure 3-7 S2.

### *3.7.2 Current flow in the brain*

We used the SimNibs toolbox to model current flow in the brain (Thielscher et al., 2015). The modelling results show that the bilateral electrode setup affected the visual cortex in both hemispheres, whereas the unilateral stimulation affected one hemisphere (left or right) only (see Figure 3-4). The SimNibs modelling approach does not provide any frequency-specific information. To determine whether the chosen tRNS frequencies (100-640 Hz) reached the cortex, we estimated the electrical field strength at frequencies between 100 and 500 Hz, in steps of 50 Hz, with Spheres 2.0 (Truong et al., 2014). The estimated electrical field strengths can polarize somatic membranes (polarization <0.3 mV per V/m electrical field (Bikson et al., 2004)) and modulate network activity at low stimulation intensities (0.2 V/m, (Deans, Powell, & Jefferys, 2007; Reato, Rahman, Bikson, & Parra, 2010)). The electrical field strengths obtained with this modelling approach are estimates of the amount of current that reaches the cortex (see Table S1). A recent paper suggests that these results might be overestimated due to possible inaccurate resistance estimates for different tissues (Huang et al., 2017), but even very low electrical fields (0.2 V/m) are able to influence network activity.

# Chapter 4: Altering brain dynamics with transcranial random noise stimulation

## 4.1 Abstract

Random noise can enhance the detectability of weak signals in nonlinear threshold systems, a phenomenon known as stochastic resonance (SR). This concept is not only applicable to excitable threshold systems but can also be applied to dynamical systems with multiple attractor states, such as binocular rivalry. Binocular rivalry can be characterized by marginally stable attractor states between which the brain switches in a spontaneous, stochastic manner. The switches are thought to be driven by a combination of neuronal adaptation and noise. In a series of 3 experiments we investigated the effect of noise on binocular rivalry dynamics by either adding noise (zero-mean Gaussian white noise) to the visual stimulus (Exp. 1) or by applying transcranial Random Noise Stimulation (tRNS 1mA, 100-640 Hz zero mean Gaussian white noise) directly to the visual cortex (Exp. 2 and Exp. 3). We used a computational model to predict the effect of noise on perceptual dominance durations. We found that adding noise significantly reduced the mixed percept duration (Exp. 1 and Exp. 2). This effect was only present for low-contrast but not for high-contrast visual stimuli. This is in line with our computational modelling predictions. Our results demonstrate that both central and peripheral noise can influence state-switching dynamics of binocular rivalry under specific conditions (e.g. low visual contrast stimuli), in line with a SR-mechanism.

Author contributions:

*Onno van der Groen:* Experimental design, Data collection, Data analysis and interpretation, Drafting of the manuscript
*Prof. Nicole Wenderoth:* Experimental design, Provided revisions to the manuscript
*Prof. Jason Mattingley:* Experimental design

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## 4.2 Introduction

Noise is detrimental for the transfer of information in linear systems (Mark D McDonnell & Abbott, 2009). However, in nonlinear systems such as the brain, noise can enhance information transfer via stochastic resonance (SR) (Mark D McDonnell & Abbott, 2009; L. M. Ward, Neiman, & Moss, 2002). SR occurs when an optimal level of noise added to a non-linear system enhances the output of the system e.g. by improving the signal-to-noise ratio (SNR) (Russell, Wilkens, & Moss, 1999b; van der Groen & Wenderoth, 2016), the signal amplitude (Manjarrez et al., 2002) or the degree of coherence within neural networks (L. M. Ward et al., 2010). In humans, the SR-effect has been observed in multiple sensory modalities when both the noise and signal are added to the peripheral nervous system (Collins et al., 1996, 1997; Simonotto, Riani, Seife, et al., 1997; Zeng et al., 2000). Recently, we have demonstrated that central mechanisms of perception are also sensitive to a SR-effect (van der Groen & Wenderoth, 2016). We showed that an optimal level of transcranial random noise stimulation (tRNS), a form of non-invasive brain stimulation, applied over visual cortex can enhance the detection performance of weak subthreshold visual stimuli.

SR not only plays a role in signal detection, however, it can also influence the dynamics of bistable-systems. One paradigm that allows the observation and measurement of how the brain dynamically transitions between different perceptual states is *binocular rivalry*. Binocular rivalry is a perceptual phenomenon that occurs when different stimuli are simultaneously presented to each eye. During binocular rivalry visual awareness switches spontaneously between the two stimuli (Levelt, 1965) so that at any given time participants perceive either one of the two images (exclusive percept) or a combination of both (mixed percept).

Models of binocular rivalry propose that it reflects a competition between neural populations coding for each image (Tong et al., 2006). The neural population coding for the dominant percept inhibits neurons that code for the suppressed image. However, over time the inhibition of the dominant population becomes weaker due to adaptation or fatigue, which allows the suppressed image to become dominant (Blake, 1989; Tong et al., 2006). This results in a deterministic anti-phase oscillation of the firing rates of the two neuronal populations (Shpiro, Moreno-Bote, Rubin, & Rinzel, 2009). When adaptation would be the only driving factor of binocular rivalry than the perception would change fairly regularly.

However, the dynamics of binocular rivalry are highly nonlinear and stochastic. Noise associated with the activity of the two neuronal populations causes a random distribution of dominance durations (Lankheet, 2006). Therefore, noise is thought to play a crucial role in the occurrence of the perceptual switches and it has even been suggested that it is an essential driving force of rivalry dynamics (Brascamp, van Ee, Noest, Jacobs, & van den Berg, 2006; Huguet, Rinzel, & Hupe, 2014). Consequently, many successful models of binocular rivalry contain a noise component to describe the rivalry dynamics (Moreno-Bote, Rinzel, & Rubin, 2007; Said & Heeger, 2013; Shpiro et al., 2009). While it has been demonstrated that rivalry dynamics can be influenced by adaptation (Roumani & Moutoussis, 2012), the effect of adding noise directly to the brain during binocular rivalry has not been empirically tested. Rivalry dynamics can conceptually be represented by a double-well energy landscape, with each well representing one of the images (see Figure 4-1). Neuronal adaptation can be represented as a driving oscillating signal that changes the energy-landscape, that is, the depth of the well. Counterintuitively, adding an optimal level of noise to this weak oscillating signal can enhance the strength of this driving signal via a SR-mechanism (L. Gammaitoni, Marchesoni, Menichella-Saetta, & Santucci, 1989; Rajasekar & Sanjuan). This can make the weak driving signal (neuronal adaptation) the main driving force of the rivalry dynamics. At a behavioural level this results in a decreased variability in time spent in a single state due to the oscillatory nature of the noise-enhanced driving signal.

Here we investigate if the attractor dynamics of binocular rivalry can be modulated by adding noise to either the visual stimulus or directly to the visual cortex with tRNS (Onorato et al., 2016; Terney et al., 2008). Three experiments were performed: In experiment 1 noise was added to the visual stimulus to test if a SR-effect is induced when noise is added to the periphery. In experiment 2 we added noise to the visual cortex with tRNS to test if central mechanisms of perception are sensitive to a SR-effect. The results of these experiments suggest that rivalry dynamics can be influenced by noise, when there are three stable states. In experiment 3 we again added the noise to the visual cortex with tRNS, however, the experimental design was optimized in order to get only two stable states. In order to make clear predictions before data collection we simulated the effect of adding noise to rivalry dynamics with a computational model (Said & Heeger, 2013). We also modelled current flow in the brain (Thielscher et al., 2015) to estimate electric field strength in our region of interest (Truong et al., 2014).

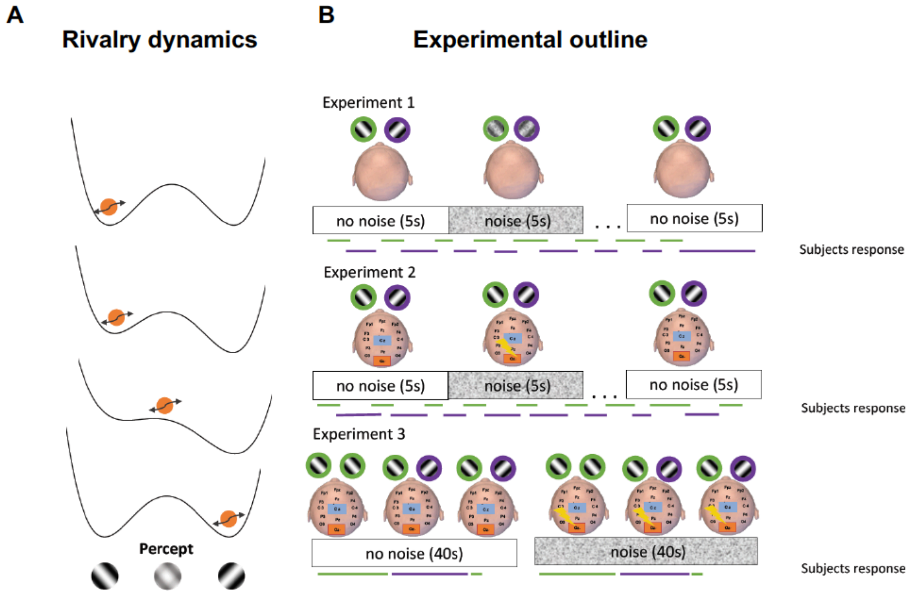

*Figure 4-1 Representation of the rivalry dynamics and methods.*
**A)** Binocular rivalry can be represented by a double-well energy landscape. The orange ball determines the current percept. Binocular rivalry is thought to be driven by adaptation and noise. Adaptation changes the landscape, meaning one of the wells becomes less shallow. Noise (arrow) causes the percept to change more quickly when the boundary between the two wells is low. **B)** Experimental outline. In experiment 1 noise (zero-mean Gaussian white noise) was applied to the visual stimulus for 5 seconds followed by 7 seconds of no stimulation. The same noise was applied to the left and right eye. The noise intensity was subthreshold for each individual participant. Experiment 2 followed the same protocol, except that the noise was applied to the visual cortex directly with tRNS (zero-mean Gaussian white noise, 100-640 Hz). In experiment 3 noise was also applied to the visual cortex with tRNS. However, two images with the same orientation were presented to each eye at the start of each trial. After a variable interval one of the two images changed orientation, causing the percept to switch. Noise was applied in blocks of 40 seconds.

## 4.3 Materials and Methods

The study was approved by the Kantonale Ethikkomission Zürich, Switzerland (KEK-ZH-Nr. 2014-0269) and by The University of Queensland Human Research Ethics Committee. Informed consent was obtained from all participants before the start of the experiment.

### *4.3.1 General procedures of experiments 1 and 2*

The data for experiments 1 and 2 were collected in Zurich. All experiments took place in a dark and quiet room. Visual stimuli (left and right tilted gratings) were generated using MATLAB version 2012b (MathWorks, Natick, USA) and the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). Stimuli were controlled by a HP Elitedesk 800 G1 running Windows 7 (2009). Stimuli were presented on a Sony CPD-G420 color monitor with a calibrated linearized output at a resolution of 1280x1024 pixels, with a refresh rate of 75 Hz. The two images were placed on the horizontal meridian to the left and right hand side of the screen on a uniform grey background (53 Cd/m$^2$). The visual stimuli were orthogonal Gaussian gratings (orientation ± 45°, diameter 3 cm, contrast 20 %, visual angle 4°, spatial-frequency 5 cycles per degree) surrounded by a white square (diameter 3.5 cm), to promote binocular fusion. Participants were seated in front of the monitor and viewed the images through a mirror stereoscope from a distance of 45 cm while resting their head on a chin rest.

Each participant performed 8 runs of binocular rivalry, each lasting 3 minutes. The task for the participants was to continuously report on a keyboard whether they perceived the left or right tilted grating or a mixture of both. In each experiment the noise was only applied in 4 runs to either the screen (exp. 1) or directly to the visual cortex with tRNS (exp. 2). The order of the noise run was randomized over participants. In these runs the noise was applied for 5 seconds followed by a 5.5 – 7 seconds interval of no stimulation, and in total 18 times per run. In each experiment participants received a total of 360 seconds visual noise (exp. 1) or tRNS (exp. 2). Participants conducted one practice run without any noise before the start of the experiment.

### *4.3.2 Experiment 1: Peri-noise condition*

In this experiment, we tested if adding dynamic noise (zero-mean Gaussian white noise) to the visual stimuli influences binocular rivalry dynamics. The same noise was applied to the left and right eye. Before the start of the experiment we determined a rough-estimate of each individual's noise threshold. Previous research demonstrated that a noise intensity corresponding to 60% of threshold effectively induces a SR-effect (van der Groen & Wenderoth, 2016). Therefore, we used a simple up-down method to estimate each individual's 60% correct noise-threshold before the experiment started. We tested two cohorts of participant, one with a low contrast visual stimulus (20% contrast, n = 10, mean age = 23) and one with a high contrast visual stimulus (70% contrast, n = 10, mean age =24). It is well established that SR only occurs for weak stimuli, therefore, we expect to observe an SR effect only for the low contrast stimuli (Collins et al., 1996, 1997; Luca Gammaitoni et al., 1998; Simonotto, Riani, Seife, et al., 1997; van der Groen & Wenderoth, 2016; Zeng et al., 2000).

### *4.3.3 Experiment 2: tRNS-V1 condition*

In this experiment, we tested the hypothesis that adding noise directly to the visual cortex with tRNS can influence rivalry dynamics. Noise was applied centrally with tRNS (100-640 Hz, zero-mean Gaussian white noise). Electrode placement was determined using the 10-20 system. The stimulation electrode was placed over the occipital region (Oz in the 10-20 EEG system) and the reference electrode over the vertex (Cz in the 10-20 EEG system). This setup has been demonstrated to be suitable for stimulation of the visual cortex (Neuling et al., 2012). Electroconductive gel was applied to the contact side of the electrode (5x7 cm) to reduce skin impedance. Electrodes were held in place with a bandage. Stimulation was delivered by a battery-driven electrical stimulator (DC-Stimulator Plus, neuroConn). An intensity of 1 mA was applied since it has been demonstrated that this intensity effectively induces a SR-effect in most subjects (van der Groen & Wenderoth, 2016). The maximum current density in this experiment was 28.57 $\mu A/cm^2$, which is within safety limits (Fertonani et al., 2015). We again tested two cohorts of participant, one where the visual stimulus had a low contrast (20% contrast, n = 15, mean age = 23) and one where the visual stimulus had a high contrast (70% contrast, n = 15, mean age = 24).

### *4.3.4 Experiment 3: tRNS-V1 follow-up with optimized design*

Data collection for this experiment took place at the Queensland Brain Institute in Brisbane, Australia. The visual stimuli in experiment 3 were the same as in experiments 1 and 2. Visual stimuli were generated using MATLAB version 2015a (MathWorks, Natick, USA) and the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). Stimuli were controlled by a Dell Precision T1700 running Windows 7 (2009). Stimuli were presented on an ASUS VG 248 QE colour monitor with a calibrated linearized output at a resolution of 1280x1024 pixels, with a refresh rate of 75 Hz. Participants (n = 15, mean age = 22) performed 8 runs, each made up of 6 x 40 second blocks. Each trial started with the two gratings presented with the same orientation in each eye (see Figure 4-1). After a variable interval (1-1.5 seconds) one of the gratings changed orientation, which results in this grating becoming the dominant percept. Over time, the percept automatically switches back to the orientation of the non-flipped grating, like in normal binocular rivalry. Therefore, in each trial two perceptual switches occurred. The first perceptual switch occurred after one of the gratings was flipped, the second perceptual switch occurred when the flipped grating lost dominance and the non-flipped grating became dominant. The amount of time the flipped grating was perceived is the dominance duration of the percept. The order in which one of the two gratings flipped was counterbalanced within each block. The task for the participants was to press the spacebar with their right hand as soon as their percept changed. After two spacebar presses or when the spacebar wasn’t pressed within 10 seconds of the flip the next trial would start. Trials where the two perceptual switches didn’t occur were excluded from analysis. Participants performed as many trials as possible within a 40 second block. In half of the blocks, tRNS was applied to the visual cortex (same electrode setup as in exp. 2) for the duration of the block. A block with tRNS-stimulation was always followed by a block without stimulation in order to reduce any possible tRNS after effects. The order of the blocks with and without tRNS were counterbalanced over participants. In 4 runs the visual stimuli had a high contrast (70%), and in 4 runs a low contrast (20%). The order of grating contrast presentation was randomized over participants.

### *4.3.5 Data analysis and statistics*

Statistical analyses were performed using SPSS (version 20.0, IBM). The same statistical procedures were applied to all 3 experiments. For each participant, we calculated the mean dominance duration for the exclusive percepts. In experiment 1 and 2 we also calculated the mixed percept dominance durations. Times where no button was pressed, or when the dominance duration was shorter than 150 ms were excluded from analysis. Dominance durations terminated by the end of a block were also not included in the analyses. In each experiment, we also calculated the number of perceptual switches. To test for the effect of the added noise, dominance durations, standard deviations and number of perceptual switches were subjected to a two-sided within-subject t-test. The $\alpha$-level was set to 0.05 for all tests.

### *4.3.6 Computational model of rivalry dynamics*

We applied a computational model to predict how noise influences the rivalry dynamics (Said & Heeger, 2013). We used a conventional binocular rivalry model which relies on competition between neurons tuned to orthogonal orientations. The model relies on mutual inhibition and it also includes a noise component. The model contains two different neuronal populations and calculates the difference in firing rate between these populations. When one population is firing fully the other population will be inhibited, resulting in the percept related to the fully firing population being dominant. When the difference in firing rate between the two populations is small then there is no winning population, resulting in a mixed percept. We introduced a criterion for mixed percepts, which was a difference in firing rate between the two neuronal populations of smaller than 0.1. In calculating mean dominance durations, we only included dominance times longer than 150 ms. In the model, we changed the strength of the visual stimulus and the amount of noise according to our experimental parameters. All other model parameters were identical to the original model parameters (Said & Heeger, 2013).

### *4.3.7 Modelling of the electric field induced by tRNS*

Modelling was used to estimate the electrical field strength in the visual cortex (Spheres 2.0 (Truong et al., 2014)). We did this for specific frequencies between 100 and 500 Hz (50 Hz steps, see table 1). We also modelled the current flow in the brain using the SIMNIBS toolbox (Thielscher et al., 2015). The modelling results show that the current reaches the brain and that it is focused on the visual cortex (Figure 4-4). Our modelled electrical field strengths (table 1) show that all frequencies reach the cortex (scaling quasi-linearly with tRNS intensity).

## 4.4 Computational modelling results

We used a traditional binocular rivalry computational model to predict the effects of adding noise to the binocular rivalry process (Figure 4-2 (Said & Heeger, 2013)). The simulation was run 100 times in order to get an estimate of the variability of the model. Adding noise during binocular rivalry increases the duration of exclusive percepts (increase of 22% - average across low and high contrasts). The strongest effect of adding noise was observed as a substantial reduction of the mixed percept (63% decrease – averaged across low and high contrasts). This magnitude of this effect was different depending on contrast intensity: there was a stronger reduction of mixed percept durations for low contrast trials (72% change) than for high contrast trials (53% change).

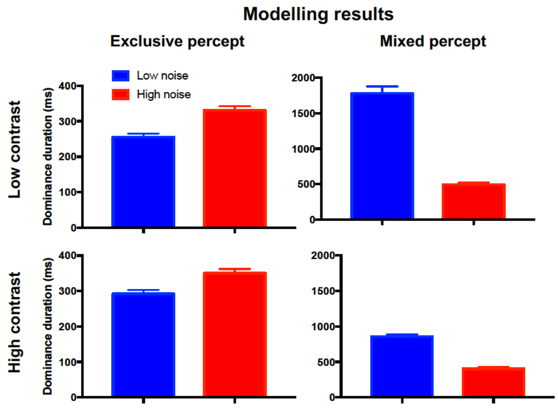

*Figure 4-2 Computational modelling results.*
We modelled the effect of adding noise to a rivalry model, and determined dominance durations of the exclusive and mixed percepts (Said & Heeger, 2013). These results indicate that adding noise to the rivalry process mainly reduces the duration of the mixed percept for low contrast visual stimuli. For the exclusive percept duration, the dominance duration increases with an increasing noise level for both the low and high contrast visual stimuli.

## 4.5 Behavioural results

Consistent with previous investigations, no participant reported awareness of the tRNS stimulation during de-briefing (Ambrus et al., 2010; Fertonani et al., 2011) .

### *4.5.1 Experiment 1*

Adding noise to the low contrast visual stimulus during binocular rivalry significantly reduced the mean dominance duration of the mixed percept ($t(9) = 2.712$, $p = 0.024$, Figure 4-3, see Figure 4-4 for individual subject data). This effect coincided with a significant reduction in the standard deviation of the mixed percept ($t(9) = 3$, $p = 0.015$). Adding noise to a high contrast visual stimulus did not affect the mixed dominance duration ($t(9) = 0.562$, $p = 0.588$) or its standard deviation ($t(9) = 0.234$, $p = 0.82$).

The exclusive percepts were not significantly affected by peripheral noise for low contrast stimuli ($t(9) = 0.789$, $p = 0.45$) or high contrast stimuli ($t(9) = 0.335$, $p = 0.75$). These results are in line with the effect predicted by the computational model. The number of perceptual switches was not affected by noise (low contrast: $t(9) = 0.65$, $p = 0.53$; high contrast: $t(9) = 0.75$, $p = 0.47$).

### *4.5.2 Experiment 2*

In experiment 2 we added noise directly to the visual cortex with tRNS and observed a similar pattern of results to experiment 1. That is, the mean mixed dominance duration of the low contrast visual stimulus was significantly reduced ($t(14) = 2.581$, $p = 0.022$, Figure 4-3, see Figure 4-4 for individual subject data). This effect coincided with a significant reduction in the standard deviation of the mixed percept ($t(14) = 2.49$, $p = 0.026$). Adding noise to a high contrast visual stimulus did not affect the mixed dominance duration ($t(14) = 1.377$, $p = 0.19$) or its standard deviation ($t(14) = 1.129$, $p = 0.278$). The exclusive percepts were not significantly affected by tRNS for the low contrast visual stimuli ($t(14) = 0.832$, $p = 0.420$) or for the high-contrast visual stimuli ($t(14) = 1.044$, $p = 0.314$). The number of perceptual switches were not affected by tRNS (low contrast: $t(14) = 0.72$, $p = 0.485$; high contrast: $t(14) = 0.813$, $p = 0.43$).

### *4.5.3 Experiment 3*

It has been suggested that adding an optimal level of noise can enhance the strength of the weak driving signal in bistable systems (Luca Gammaitoni et al., 1998). However, in experiments 1 and 2 the system had three-marginally stable states due to the mixed percept state. Therefore, we ran a follow-up experiment with an optimized design with only two stable states in a different cohort of participants. We had to exclude two participants because they were not able to do the task. Our results did not reveal any significant effect of noise on the exclusive percept duration (low contrast: t(12) = 0.676, p = 0.51; high contrast: t(12) = 0.19, p = 0.85) or the number of perceptual switches (low contrast: t(12) = 1.26, p = 0.23; high contrast: t(12) = 1.01, p = 0.33). Taken together, our results suggest that adding noise to binocular rivalry can only effect the dynamics of the mixed percepts but not of exclusive percepts.

The modelling results show that that all stimulation frequencies were transmitted to the brain and that the applied current applied is sufficiently strong to reach the cortex (scaling quasi-linearly with tRNS intensity). The current is mainly focused on the visual cortex, however, there is spread to other brain areas.

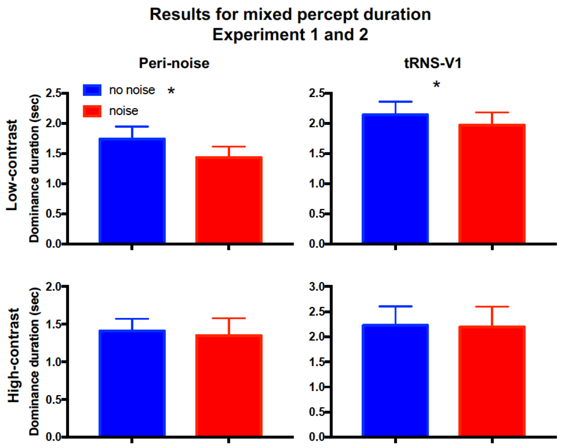

*Figure 4-3 Behavioural results of experiments one and two.*
Adding noise significantly reduces the dominance duration of the mixed percept for low contrast visual stimuli. There is no significant effect of adding noise on the dominance duration of the exclusive percept. Error bars represent SEM. *p < 0.05

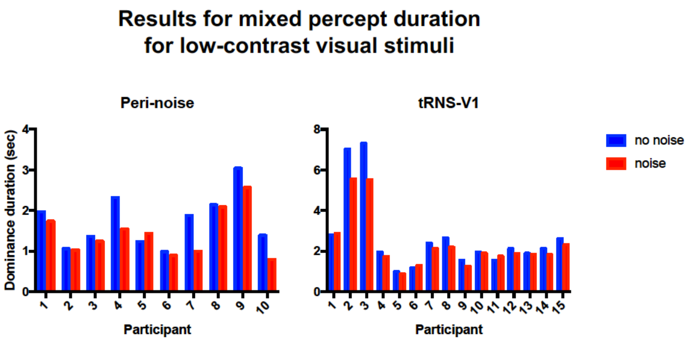

*Figure 4-4 Individual effects on mixed percept duration.*
The individual data for the low-contrast visual stimuli are displayed. We can see that the mixed percept duration decreases in most participants when noise is added to the screen or directly to V1 with tRNS.

**A.**

| | *Intensity(mA)* |
|---|---|
| *Frequency (HZ)* | 1 mA |
| *100 Hz* | 2.2 V/m |
| *150 Hz* | 2 V/m |
| *200 Hz* | 2.2 V/m |
| *250 Hz* | 2.2 V/m |
| *300 Hz* | 2.1 V/m |
| *350 HZ* | 2.1 V/m |
| *400 Hz* | 2.1 V/m |
| *450 Hz* | 2.2 V/m |
| *500 Hz* | 2.2 V/m |

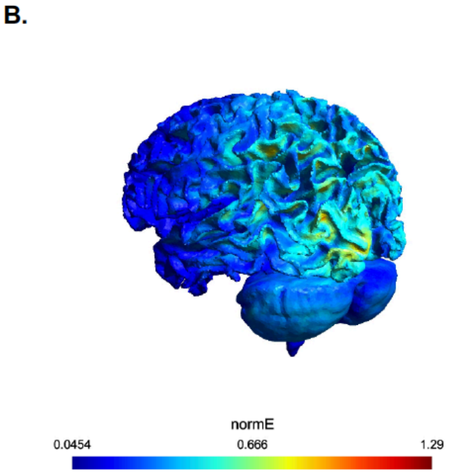

*Figure 4-5 Electrical field strength and current flow modelling results.*
**A)** Modelled electric field strength (V/m) for different transcranial electrical current stimulation (tECSs) intensities (mA) and frequencies (Hz). **B)** Modelled current flow in the brain. This image shows where the current flows in the brain. It does not provide any information on the frequency characteristics, therefore, we modelled this separately (see table on the left).

## Conclusion and Discussion

Our results demonstrate for the first time that adding noise to a visual stimulus during binocular rivalry can significantly reduce mixed percept durations. The same results were obtained when noise was added to the visual cortex directly with tRNS. These effects coincided with a significant reduction in the standard deviation of the mixed percept duration, suggesting less variability in the mixed dominance durations. This effect only occurred when the visual stimuli had a low contrast. These results were consistent with the predictions made by a computational binocular rivalry model (see Figure 4-2). Exclusive percept dominance durations in experiment 1, 2 and 3 were not affected by noise.

### *4.5.1 The difference between peripheral and central noise*

Adding noise to the visual stimuli (peripheral noise) resulted in the same behavioural results as adding noise to the brain directly with tRNS (central noise), that is, a significant reduction in mixed percept duration when the stimuli had a low contrast. No effect was observed when the stimuli were presented with a high contrast, suggesting that the stimulus contrast is a crucial parameter. Previously we have shown that noise added peripherally and centrally can both enhance performance on a contrast detection task (van der Groen & Wenderoth, 2016) for weak visual stimuli according to a SR-effect. Unpublished findings suggest that this is due to an increase in the quality of the signal representation in the brain. An important difference between these two noise application methods is the location in the nervous system where they can influence the visual processing for the first time. Peripheral noise likely influences visual processing at the receptor level, before the visual stimuli are processed by the brain. tRNS on the other hand influences visual processing at the cortical level. By applying tRNS during binocular rivalry we show that noise at a cortical level can causally influence mixed percept duration.

The processes underlying the occurrences of mixed percept during binocular rivalry are unclear, however, a possible mechanism involves changes in the strength of mutual inhibition between the two neuronal pools, each coding for a different percept (Hollins, 1980; Klink, Brascamp, Blake, & van Wezel, 2010). It is thought that stronger stimuli (stimuli with a higher signal-to-noise ratio) result in an increase in mutual inhibition, which leads to a reduction of the mixed percept duration (Hollins, 1980). Our noise could have strengthened mutual inhibition due to an increase in the SNR of the stimulus representation in the brain. Related to this finding, a recent study demonstrated that alcohol intake enhances mixed percept duration (Cao, Zhuang, Kang, Hong, & King, 2016). Further, it has been shown in cats that alcohol reduces the signal-to-noise ratio (i.e. increases noise) in primary visual cortex (Chen, Xia, Li, & Zhou, 2010). In our study we likely increased the SNR in visual cortex, resulting in a reduction of mixed percept duration.

Another possible mechanism that effects mixed percept duration is a change in the balance between excitatory and inhibitory neural activity (Said, Egan, Minshew, Behrmann, & Heeger, 2013). An imbalance between cortical excitation and inhibition is an important factor in many autism spectrum disorder (ASD) models (Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker, 2013). However, it is still not known whether lower biological noise levels are also involved in ASD (Davis & Plaisted-Grant, 2015). Interestingly, our finding that only mixed percepts are sensitive to a noise effect is supported by a study into binocular rivalry in ASD (Robertson et al., 2013). Robertson and colleagues did not find any difference between healthy controls and people with ASD on exclusive percept duration. It is known that tRNS is able to enhance cortical excitability after 4 minutes of continuous stimulation (Chaieb, Paulus, & Antal, 2011), which results in a change in the excitation-inhibition balance. However, with our design it is unlikely that we changed cortical excitability because of the relatively short tRNS application durations. Moreover, after each tRNS block there was always a block without tRNS to reduce the likelihood of any after effects. Besides this, adding noise to the visual stimulus resulted in similar effects, and as far as we know cortical excitability cannot be modulated by peripheral noise. Therefore, our results are most likely explained by a SR-effect that modulates perceived stimulus contrast.

In experiment 3 we did not find any effect of noise on rivalry dynamics. This is likely not because binocular rivalry is insensitive to a SR-effect, since it has been previously demonstrated that binocular rivalry is sensitive to a SR-mechanism (Kim, Grabowecky, & Suzuki, 2006). In contrast to our study, Kim and colleagues did not add noise to the rivalry process, but changed the strength of the driving signal by changing the contrast of the two images in counter phase. The idea is that SR will occur when the driving signal matches with biological noise levels. The reason there is no noise effect on the dominance duration of the exclusive percepts in our study could be because the noise added in the current study might not be optimal to introduce a SR-effect in a bistable system. The noise properties we applied were based on the findings of our previous study (van der Groen & Wenderoth, 2016) where we demonstrated that tRNS and peripheral noise are able to enhance performance on a contrast detection task. Theoretically, in bistable systems the optimal noise level to influence the dynamics can be calculated when the period of the external driving force is known (Luca Gammaitoni et al., 1998). In binocular rivalry however, the period of the driving force is not exactly known due to the stochasticity of the rivalry dynamics. This stochasticity is due to biological noise levels that have an effect on the rivalry dynamics (Brascamp et al., 2006; Moreno-Bote et al., 2007; Shpiro et al., 2009).

### *4.5.2 Current flow in the brain*

In order to determine whether tRNS induced electrical noise in the cortex we used simulations based on a spherical head model (Truong et al., 2014). The modelling results demonstrated that our stimulation induced an electrical field around 2 V/m and that all frequencies were transmitted to the brain. With tRNS a mix of alternating currents (AC) is applied to the cortex. It has been calculated that an electrical field strength of 1 V/m of 100 Hz AC can polarize a neuron by only 50μV (Deans et al., 2007). This estimated field strength is too small to directly depolarize neurons. However, it is thought that this signal can be amplified by stimulating more neurons simultaneously (Francis, Gluckman, & Schiff, 2003). This small depolarization may be enough to elicit action potentials (APs) in neurons that are close to threshold, which results in a weak stimulus reaching the threshold AP generation earlier.

### *4.5.3 Neuronal correlates*

Although it is still debated where in the brain binocular rivalry is resolved, we targeted the visual cortex. Our current spread modelling results (Figure 4-4) demonstrate that our setup was suitable for stimulation of the visual cortex. The reason we targeted the visual cortex is because neuronal activity in primary visual cortex (V1) is linked to the subjective percept during binocular rivalry (Lee, Blake, & Heeger, 2007; Leopold & Logothetis, 1996; Polonsky, Blake, Braun, & Heeger, 2000). Changes in higher order brain areas, like frontoparietal activity, are thought to be the result of perceptual alternations rather than the cause of the perceptual alternations (Knapen, Brascamp, Pearson, van Ee, & Blake, 2011). However, this is still an area of debate as there is also evidence that frontoparietal activity might play a causal role (Carmel, Walsh, Lavie, & Rees, 2010; Kanai, Carmel, Bahrami, & Rees, 2011; Zaretskaya, Thielscher, Logothetis, & Bartels, 2010). Evidence that mixed percepts may be more influenced by low-level visual processes rather than higher processes (Antinori, Carter, & Smillie, 2017; Blake, Oshea, & Mueller, 1992) supports the interpretation that our effect is driven by stimulation of these low-level visual cortices.

In conclusion, our results are the first to demonstrate that mixed percept durations can be altered by applying noise to the visual cortex directly with tRNS, likely due to an enhancement of stimulus contrast. Our results open up new ways of manipulating noise levels within the brain and provide a better understanding of the effect of noise on the brain when it is in a dynamical state.

# Chapter 5: Discussion and Conclusion

In this thesis we replicated previous work that showed that the addition of noise to a visual stimulus can enhance detection performance via a SR-mechanism. Moreover, we demonstrated for the first time that a SR-effect can be induced by adding noise to the brain directly with tRNS, in line with non-dynamical SR principles (Chapter two). The results of this study demonstrate that the human brain is sensitive to a SR-effect, however, they do not provide insight into the underlying mechanisms. Therefore, in Chapter three computational modelling was applied to a behavioural task. This modelling permitted further investigation into which part of the decision-making processing was sensitive to a SR-effect. The results demonstrate that decision-making can be improved with tRNS by enhancing the representation of the stimulus quality. Chapter four investigated if a SR-effect could be induced with tRNS according to dynamical-SR principles. To this end participants conducted a task in which the brain was in a dynamical state. The results of this study show that there is an effect of tRNS on the stochastic dynamics, however, this effect can be entirely explained by non-dynamical SR-effects. These findings are discussed in more detail below in addition to an exploration of the limitations and implications of the results.

## 5.1 Non-dynamical SR-effect induced with tRNS

First of all, we will discuss the findings of the study outlined in Chapters two and three, because both involve non-dynamical SR. Previous research has suggested that central mechanisms of perception are sensitive to SR (Kitajo, Nozaki, Ward, & Yamamoto, 2003a; Lugo et al., 2008; Manjarrez et al., 2007). By adding tRNS to the brain directly we are the first to show causal evidence for a SR-effect in central mechanisms of perception. The findings are not only interesting for perception research, but are also of interest to the brain-stimulation community. Previous tRNS-studies have suggested that SR-effects may contribute to the physiological and behavioural effects found after prolonged tRNS-stimulation (Chaieb et al., 2011; Fertonani et al., 2011; Terney et al., 2008). These studies were not designed to detect online SR-effects and it is likely that their findings are related to the initiation of LTP- mechanisms due to the longer stimulation periods. Our experimental designs, on the other hand, were specifically designed to pick up online SR-effects. The results also provide support for the notion that behavioural effects of online-NIBS can be explained as a modulation of neural activity that changes the relationship between signal and noise (C. Miniussi et al., 2013). The improvements in behavioural measures demonstrate that adding tRNS to the brain can have an immediate causal effect on behaviour. The results of the second study outlined in Chapter three extend these findings by showing that the tRNS effect is not limited to a contrast-detection task. In applying DDM, it was shown that when an optimal level of noise was added to the visual cortex, the drift rate increased. The drift rate in DDM is thought to represent the quality of the stimulus or SNR of the sensory evidence (R. Ratcliff & McKoon, 2008). This finding is in line with the SR-literature, where an optimal level of noise added to a weak stimulus enhances the system output, where in this case the system output is the stimulus representation in the brain.

We know from previous research that repetitive practice on a perceptual task can also enhance the signal quality of trained stimuli (Ahissar & Hochstein, 2004). This learning effect has been shown to increase the drift-rate after training for at least 20 hours (Jehee, Ling, Swisher, van Bergen, & Tong, 2012). It is possible that learning effects contribute to our results, however, it is unlikely that this is the underlying cause of improved performance in our studies due to the short exposure times. Nevertheless, it is possible that learning could be optimized through an immediate enhancement of the quality of the signal with tRNS without the need for a long learning process. It has indeed been demonstrated that performance in a perceptual learning task increases when tRNS is applied during learning compared to sham and other tCS-stimulation protocols (Fertonani et al., 2011), and also that arithmetic learning can be enhanced by applying tRNS during the learning processes (Popescu et al., 2016). Interestingly, in the last study the effect only occurred for difficult stimuli, which is again in accordance with SR theory.

## 5.2 Underlying mechanisms

The underlying neuronal mechanism for the observed SR-effect, induced both by peripheral noise and tRNS, is not clear. To the best of our knowledge it has never been tested directly how noise added to neurons directly influences the signal representation but we do know from animal studies that neurons in the primary visual cortex are sensitive to a SR-mechanism, e.g. there is an increase in SNR when an optimal level of noise is applied to the visual stimulus (Funke et al., 2007). The increase in SNR is likely due to the activation of voltage-gated sodium channels by noise (Onorato et al., 2016). Remember that the generation of APs is an all-or-nothing phenomenon, meaning that once the threshold is crossed there will always be an AP. When the noise activates voltage-gated sodium channels, a weak signal might be enough to cross the threshold for AP generation. Funke and colleagues (2007) also showed that the

SNR only decreased slightly when excessive noise was added (Funke et al., 2007), a pattern also reflected in our results where we do not see a reduction in detection performance at high noise intensities.

An important note here is that our behavioural results are likely due to network effects of SR and not due to the effect of noise on one single neuron. In order to add noise to neurons in the cortex with tRNS the current must first of all reach those neurons. The estimated electrical field strengths in our studies were strong enough to weakly polarize somatic membranes (polarization <0.3 mV per V/m electrical field (Bikson et al., 2004)) and modulate network activity (occurs with a minimum of 0.2 V/m, (Deans et al., 2007; Reato et al., 2010)). In neuronal networks, a series of neurons are interconnected and as such the noise is propagated along these channels. Noise in these networks can increase due to nonlinear computations and network interaction (Faisal et al., 2008; Laughlin & Sejnowski, 2003). One way to overcome this noise build up is to take the average over a population of neurons and reduce redundant information (Faisal et al., 2008). However, in our studies one common source of noise was applied to the brain and was likely correlated between neurons. Therefore, the noise effect cannot be averaged out and because of this, a SR-effect can still occur at a network level.

A possible working mechanisms could be that tRNS increases the number of neuronal assemblies activated by a weak stimulus by bringing neurons closer to the firing threshold, in line with the effect observed at a neuronal level described above (Funke et al., 2007). An alternative theory regarding the underlying mechanism of SR is that adding an optimal level of noise to a weak stimulus enhances the synchronization between different brain areas through amplification of subthreshold oscillatory activity (Antal & Herrmann, 2016; Kitajo et al., 2007; Kitajo, Yamanaka, Nozaki, Ward, & Yamamoto, 2004; L. M. Ward et al., 2010). It has not yet been tested whether tRNS is able to influence neuronal oscillations. It is possible that adding an optimal level of noise may induce neuronal firing during the peak of the driving signal when a neuron receives a weak oscillatory input. In this way the weak oscillatory signal is enhanced (Ermentrout, Galan, & Urban, 2008). This synchronization increase would then optimise communication between brain areas (Fries, 2005). This idea is further described by Ward (L. M. Ward, 2009). Based on our data we cannot confirm or exclude the possibility that the enhancement of neuronal communication with tRNS plays a role in our behavioural findings. However, it is highly possible, in study one at least, that neuronal synchronisation underlies the behavioural effect. An enhancement of neuronal synchronisation seems to be related with an increase in attention (Kim, Grabowecky, Paller, Muthu, & Suzuki, 2007) and it has been suggested that attentional mechanisms on a contrast detection task are sensitive to a SR-effect (Kitajo, Yamanaka, Ward, & Yamamoto, 2006). In study one the visual stimulus was presented for a relatively short time, which makes it likely that attention played a significant role. In the second study, it could also be that an increase in attention is the underlying mechanism because it has been demonstrated that increases in attention enhances the performance on a motion detection task (Nishida, 2011).

## 5.3 Dynamical SR-effects

In Chapter four we investigated if a SR-effect can be induced in adherence with non-dynamical SR principles using a binocular rivalry task, a task which results in the brain entering a dynamical state. One study demonstrated that binocular rivalry dynamics are sensitive to a SR-mechanism (Kim et al., 2006). In this study, they did not influence the noise levels, but changed the driving signal by weak periodic contrast modulations at a specific frequency. Their idea was that ‘biological noise’ levels can induce a SR-effect when the driving signal has the optimal frequency. Their results demonstrated that there is a peak in the perceptual dominance duration distribution when a signal with an optimal driving frequency is applied. In our data, this peak in dominance duration was not observed. Our data show that the mixed percept duration is significantly affected by the noise, but only when the stimuli are of low contrast. There are a few possibilities as to why similar effects to the study by Kim and colleagues were not found. First of all, it is currently unknown how ‘biological noise’ interacts with tRNS in this task. The possibilities will be discussed in the next paragraph. Second, the experiment design used in the present study only tested one tRNS intensity, namely the intensity shown to most effectively induce a SR-effect in experiment one. It is possible that the optimal tRNS intensity in non-dynamical systems (Chapter two) is not the same as the optimal tRNS intensity in dynamical-systems (Chapter four) and that is why we did not observe similar effects. Theoretically it is possible to calculate the optimal intensity when one knows the period of the external driving force. In binocular rivalry, however, the period of the driving force is not known due to the stochasticity of the rivalry dynamics. This stochasticity is due to biological noise levels that have an effect on the rivalry dynamics (Brascamp et al., 2006; Moreno-Bote et al., 2007; Shpiro et al., 2009). Therefore, it would be worth testing a variety of tRNS intensities in future follow-up work to allow for this individual variation.

In our first study (Chapter two), we individualized the visual noise intensities in relation to each participant's noise threshold. However, this was not possible when noise was added to the cortex with tRNS in the experiment outlined in Chapters three and four because currently it is not possible to determine how much noise is presented in the brain. In the next section we will closer examine the role of biological noise to see what influences this may have had on SR effects in these experiments.

## 5.4 The role of biological noise levels on individual differences

Previous research has suggested that biological and external noise levels likely interact with each other (Aihara, Kitajo, Nozaki, & Yamamoto, 2008). Individuals with a low biological noise level may need a higher tRNS intensity to induce a SR-effect, and vice versa. It may be the case that when biological noise levels are high, that the intrinsic noise present in the system is equal or higher than the optimal noise level for SR to occur (Aihara et al., 2008). Therefore, some participants may not show any SR-effect, and this is possibly the cause of the large individual differences in optimal tRNS noise levels observed in the experiment outlined in Chapter two. Here the optimal tRNS noise level was determined based on the maximum improvement. In Chapter three there was less individual variability in optimal tRNS noise levels. This is most likely due to the fact that in this experiment the SNR (i.e. the amount of coherent moving dots compared to the amount of randomly moving dots) was fixed for each stimulus, whereas in the previous experiment, the SNR was only dependent on the internal noise level. The single intensity used in Chapter four may not have been the optimal noise level for everyone, and therefore an effect of noise on exclusive percept duration was not seen. Note that in this case biological noise refers to intrinsic variability at the neuronal level (Faisal et al., 2008).

It may be argued that sensory information processing uses neuronal variability to enhance signal processing as a form of "biological noise" or that neuronal systems optimize biological noise levels to enhance information transfer (Moss, 2004). It is conceptually difficult to know when to classify neuronal variability as noise and this is unrelated to the inducement of a SR effect with added noise from an external source. Additionally, when such neuronal variability is not correlated over many neurons, it is likely averaged out.

## 5.5 Study limitations and caveats

In Chapters two and three we reported measures of the amount of correct responses but not d'. In our study we did not calculate any changes in the decision criterion. However, it is highly unlikely that our results are driven by a change in decision criterion rather than by a change in sensitivity. This is firstly because we implemented a widely used 2-IFC paradigm. It has been shown that the performance outcome in a 2-IFC paradigm is equivalent to an observer using an unbiased decision criterion (Green & Swets, 1974) . Therefore, the performance measure is directly reflective of the sensory sensitivity. Secondly, tRNS only influenced subthreshold stimuli when an optimal level of noise was applied to the visual cortex and the enhancement did not occur when noise was applied to frontal areas. This is supportive of our claim that tRNS enhances sensitivity rather than inducing a change in criterion because it is unlikely that the criterion changes in such a specific way.

In this thesis, physiological measures of the SR-effect induced by tRNS were not collected. Currently it is not possible to record EEG and tRNS at the same time due to technical limitations, therefore the online-effects of tRNS on neuronal dynamics cannot be measured with EEG. For this reason, the study outlined in Chapter three used computational modelling to gain further insight into the underlying mechanisms involved. It would, however, be possible to combine tRNS with fMRI in order to investigate the neurophysiological effects. If tRNS can indeed enhance cortical synchronisation than we should be able to detect this with fMRI. Besides this, fMRI also allows us to investigate if and how neuronal variability changes when tRNS is applied. An increase in neuronal variability will only occur when tRNS induces neuronal variability, that is, adds noise in the brain. By using fMRI we will be able to pinpoint to the underlying physiological mechanism of our observed behavioural effects.

In each of our studies tRNS was only applied in the high-frequency range because this has been demonstrated to effectively influence neuronal processing. This is likely due to the time constant of cell bodies and dendrites (Kandel et al., 2000). It is therefore unlikely that lower frequencies can induce a SR-effect. However, whether or not different waveforms have a larger effect is yet to be investigated. It is known that different classes of neurons are activated at different stimulation frequencies (Freeman, Eddington, Rizzo, & Fried, 2010; Twyford & Fried, 2016). It could be that the frequency range applied was ideal to stimulate cortical neurons involved in our studies. Further research is needed to allow for more targeted stimulation of specific neuronal populations.

The majority of research into SR focusses on perception, however, it is unclear if SR-effects can be elicited in other cognitive domains. One study measured the effect of auditory noise stimulation on a variety of cognitive tasks (Herweg & Bunzeck, 2015) and found no general effect of noise on cognition. The present thesis is limited to investigations into the effect of tRNS on lower level visual processing. Whether a SR-effect can be induced with tRNS when higher order areas are stimulated is not known. A few studies have investigated the effect of tRNS on higher cognitive processes: tRNS over DLPFC does not seem to enhance performance on working memory (Holmes, Byrne, Gathercole, & Ewbank, 2016; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011), while tRNS over DLPFC did enhance performance on arithmetical tasks, but only for difficult trials, which might be indicative of a SR-effect. Although a cognitive task (decision-making) was used in our second experiment (Chapter three), the performance improvement was achieved by enhancing the sensory information on which the decision was based. In this way, higher cognitive processes can be optimized by enhancing lower level sensory input.

## 5.7 Implications and future research

This thesis presented work from three studies. The results provide convincing evidence that central sensory processing can be enhanced by adding noise directly to the CNS with tRNS. The enhancing effect is not only limited to a contrast detection task, but it can also enhance the signal quality of a full contrast stimulus. This enhanced sensory information can be used to improve performance on a decision task. Noise added to a dynamical system can influence neuronal dynamics, but only when specific conditions are met.

The neurophysiological mechanisms underlying our behavioural effects are currently unknown since there is a lack of knowledge about the working mechanism of tRNS. It has been shown that adding noise to cell slices causes repetitive opening of sodium channels (Bromm, 1968; Schoen & Fromherz, 2008). In our current work, we are adding noise to a large part of the brain (e.g. see figure 3-4) that consists of many interconnected neurons. These interconnected neurons make up brain networks which regulate behaviour. Therefore, to predict the behavioural outcome of our random noise stimulation we need to consider the effects of noise at a network level (Pena-Gomez et al., 2012; Singh & Fawcett, 2008). By understanding the effects at a network level, we can optimise stimulation protocols to improve behaviour. There are studies which modelled neuronal and network responses to added noise (M. D. McDonnell & Ward, 2011), however, it is unclear if adding external noise, e.g. with tRNS, is comparable with the effects of the added noise in these models. Therefore, further animal studies are required. During electrical stimulation with random noise in animals, changes in behaviour and neuronal processing should be assessed at both cellular and network levels. Based on data obtained in animal studies we could then improve the models in order to get a better understanding of the effect of central noise on human behaviour (de Berker, Bikson, & Bestmann, 2013; M. D. McDonnell & Ward, 2011). Besides animal studies, imaging studies in humans are also required in order to investigate the working mechanisms of tRNS. This can be done, for example, by combining tRNS with fMRI or fNIRS. One approach would be to investigate if tRNS increases neuronal variability, since it has been suggested that this is a key parameter in models of stochastic resonance (Dinstein, Heeger, & Behrmann, 2015; Garrett, McIntosh, & Grady, 2011).

An interesting follow up study would be to investigate if the SR-effect can also be induced in the motor system. To do this, different transcranial magnetic stimulation (TMS) protocols could be used as an outcome measure of the online-effects of tRNS. A first step would be to test if the amplitude of motor evoked potentials (MEPs, a measure of cortical excitability) is dependent on the amount of noise that is added to the brain with tRNS. A stochastic resonance effect would predict that when a weak TMS pulse is applied, adding noise can increase MEP amplitude, however, when the TMS pulse is strong the noise should not increase the MEP amplitude. Follow up experiments could use different TMS protocols to investigate, for example, the effect of tRNS on cortical inhibition (by using the SICI protocol (Carlo Miniussi, Paulus, & Rossini, 2012)).

The possibilities in clinical research extend to investigating SR-effects in clinical populations with sensory processing impairments. We have shown that it is possible to enhance sensory perception performance via a SR mechanism by applying tRNS to the brain directly. Sensory feedback is a crucial part of the neurological rehabilitation process, as it was shown that sensory changes drive subsequent learning behaviour in the motor cortex (Rosenkranz & Rothwell, 2012). A first step would be to investigate if sensory perception and proprioception can be enhanced by tRNS in stroke survivors.

In the introduction, we have seen that sensory perception can be enhanced with different brain stimulation methods. Interestingly, it has been suggested that tRNS can increase neuronal synchronization between different brain areas, which would be the same underlying working mechanism causing the increased cognitive functioning in people with meditation experience. It would therefore be interesting to investigate if the SR-effect can be induced in practioners of regular meditation practices. One benefit of tRNS over TMS and meditation training is that the effect size of enhancing visual perception with tRNS (Cohen's $d = 0.77$) is larger than the effect size of TMS (Cohen's $d = 0.47$) and meditation training (Cohen's $d = 0.63$). An additional benefit of tRNS compared to TMS is that it is easier to apply, and in principle, people could apply it themselves at home. Compared to other tCS methods, the effects of tRNS also seem to have a greater enhancement on perceptual learning (Fertonani et al., 2011). Moreover, the effect of tRNS also seem to increase learning performance more compared to sham stimulation (Fertonani et al., 2011), making tRNS an attractive tool in neurorehabilitation training. Therefore, tRNS seems to be a superior method to induce a behavioural enhancing effect.

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