Aus der Klinik für Neurologie mit Experimenteller Neurologie der
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DISSERTATION

Unconscious Modulators of Somatosensory Perception

Unbewusste Modulatoren der somatosensorischen Wahrnehmung

zur Erlangung des akademischen Grades

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List of Abbreviations

2AFC	Two-Alternative Forced Choice
CNS	Central Nervous System
ECG	Electrocardiography
EEG	Electroencephalography
ENS	Electrical Noise Signal
ERD	Event-Related Desynchronization
ERS	Event-Related Synchronization
fMRI	functional Magnetic Resonance Imaging
HEP	Heart-Evoked Potential
Mu Rhythm	Sensorimotor alpha Rhythm
NT	Near Threshold
SEP	Somatosensory Evoked Potential
SNR	Signal to Noise Ratio
SR	Stochastic Resonance
SS	Somatosensory
SSSEP	Somatosensory Steady-State Evoked Potential

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Summary

Abstract (English)

It is intriguing that perception of the same stimulus can vary profoundly from trial to trial. For example, it has been shown in many studies that weak, so-called “near-threshold stimuli” are sometimes consciously perceived and sometimes not. In my thesis, I have been investigating factors which underlie this profound perceptual variability in the somatosensory domain. Together with my colleagues, I performed three studies in which we tested three different types of presumed non-conscious modulators of somatosensory perception.

In the first – behavioral - study, we investigated how the presence of subliminal noise during a peripheral somatosensory stimulation influences perception. Counter-intuitively, we found that peripheral noise can even improve perception of weak somatosensory stimuli. In our interpretation, this occurs most likely due to “stochastic resonance” effects (Study I: Iliopoulos et al. 2014).

In the second – behavioral and EEG - study, we tested the effect of different forms of pulsed subliminal stimulation (single pulses versus pulse trains) on brain rhythms and somatosensory perception. Following-up on previous results of our group, we tested the hypothesis that subliminal pulsed stimulation impairs perception of subsequent stimuli via centrally enhanced Mu rhythm. Interestingly, the main result of this study was that trains of subliminal stimuli indeed inhibited subsequent somatosensory detection, however, - in contrast to our previous findings for single pulses – trains were associated with decreased Mu rhythm. We conclude that central rhythms most likely play a role in mediating the perceptual modulation of peripheral subliminal stimuli, however, the relationship is more complex than previously assumed (Study II: Iliopoulos et al. 2020).

In the third study, we examined the influence of interoceptive signaling, especially from the heart, on somatosensory perception. The hypothesis was that the cardiac phase (systole versus diastole) and the so-called heart-evoked potential (HEP) would modulate somatosensory perception. Indeed, our study showed that somatosensory perception was better during diastole than during systole and detection performance declined as the amplitude of the HEP increased. Our interpretation of the former effect assumes that all events which occur simultaneously with the “pulse” are assumed by the brain to be pulse-synchronous peripheral noise and therefore suppressed. Our interpretation of the latter effect (HEP) assumes that HEP is a marker of the relative balance between interoception and exteroception (Study III: Al et al. 2020).

In conclusion, in the studies which form the basis for my thesis, we have shown that somatosensory perception is modulated by peripheral effects (modes of peripheral stimulation, peripheral noise), central effects (Mu rhythm) and interoceptive signals from the heart. The precise interplay between these modulators is an exciting research topic for future studies.

Abstrakt (Deutsch)

Interessanterweise kann die Wahrnehmung desselben Reizes von Augenblick zu Augenblick so stark variieren, dass dieser manchmal bewusst wahrgenommen wird und manchmal nicht. In meiner Dissertation habe ich Faktoren untersucht, die dieser Wahrnehmungsvariabilität im somatosensorischen (SS) System zugrunde liegen. Mit meinen Kollegen habe ich drei Studien durchgeführt, in denen wir verschiedene mutmaßlich unbewusste Modulatoren der SS-Wahrnehmung untersuchten.

In der ersten Studie untersuchten wir, wie die Wahrnehmung peripherer SS-Reize durch unterschwelliges Rauschen beeinflusst wird. Wir konnten zeigen, dass peripheres Rauschen die Wahrnehmung schwacher Reize verbessert. Dies ist ein Hinweis auf das Vorliegen von "stochastischen Resonanzeffekten" (Studie I: Iliopoulos et al. 2014).

In der zweiten Studie, die neben behavioralen Messungen auch elektroencephalographische (EEG) Messungen umfasste, testeten wir die Auswirkung verschiedener Formen gepulster unterschwelliger elektrischer Fingerstimulationen (Einzelpulse gegen Pulsserien) auf die Wahrnehmung und auf Hirn-rhythmen. Ausgehend von früheren Ergebnissen unserer Arbeitsgruppe überprüften wir, ob repetitive subliminale Stimulationen die Wahrnehmung nachfolgender Reize über einen zentral verstärkten Mu-Rhythmus beeinträchtigen. Das Ergebnis dieser Studie war, dass Serien unterschwelliger Reize tatsächlich die nachfolgende SS-Wahrnehmung hemmten, jedoch - im Gegensatz zu früheren Ergebnissen für Einzelimpulse – die Reizserien mit einem verringerten Mu-Rhythmus verbunden waren. Daraus schließen wir, dass zentrale Rhythmen höchstwahrscheinlich eine Rolle bei der Wahrnehmungsmodulation durch periphere unterschwellige Reize spielen, dass aber der Zusammenhang zwischen beiden komplexer ist als bisher vermutet (Studie II: Iliopoulos et al. 2020).

In der dritten Studie untersuchten wir den Einfluss interozeptiver Signale aus dem Herzen auf die SS-Wahrnehmung. Die Hypothese war, dass die Herzphase und das so genannte Herz-evozierte Potenzial (HEP) die SS-Wahrnehmung modulieren. Wir zeigten, dass die SS-Wahrnehmung während der Diastole besser war als während der Systole und dass die Wahrnehmung in umgekehrtem Verhältnis zur Amplitude des vorausgehenden HEP stand. Für den ersten Effekt legen unsere Daten nahe, dass alle Ereignisse, die zusammen mit der Pulswelle auftreten, vom Gehirn als puls-synchrones peripheres Rauschen angenommen und daher unterdrückt werden. Der zweite Befund wird in Übereinstimmung mit der Literatur am besten dadurch erklärt, dass das HEP ein Marker für das relative Gleichgewicht zwischen Interozeption und Exterozeption darstellt (Studie III: Al et al. 2020).

Zusammenfassend zeigen die Ergebnisse dieser Arbeit, wie die SS-Wahrnehmung durch periphere Effekte (Art der Stimulation, Rauschen), zentrale Effekte (Mu-Rhythmus) und interozeptive Signale des Herzens moduliert wird. Das genaue Zusammenspiel zwischen diesen Modulatoren ist ein spannendes Forschungsthema für zukünftige Studien.

1. Introduction

Understanding the neuronal mechanisms that give rise to conscious experience has been one of the central problems in the history of neuroscience. Approximately 130 years after the first empirical reports on non-conscious processing of weak external stimuli (Peirce and Jastrow 1885; Sidis 1898; Stroh et al. 1908), nowadays the general notion is that only a small part of external sensory input reaches awareness. The access of an external stimulus to consciousness is influenced by properties of peripheral stimulation (e.g., strength of sensory input, noise), ongoing spontaneous cortical activity, and interoceptive afferent signals (the most salient being cardiac-related activity). For the somatosensory system, both peripheral (peri-threshold external stimuli as well as noise) (Collins et al. 1997) and cardiac signals (Edwards et al. 2009) have been shown to modulate the processing of a stimulus. Comprehensively, external stimulation, interoceptive signals, cortical oscillations and finally noise, all together appear to influence significantly the generation and/or the modulation of the somatosensory neural response and its access to consciousness. To identify time-specific mechanisms by which these factors affect behavior and the neural response, in our paradigms we systematically varied the temporal pattern of the applied (subliminal) stimulation. Different types of stimuli were implemented ranging from random/irregular (noise and time-jittered single pulse stimulation) to periodical (pulse trains). My thesis builds on three studies in which three factors that modulate perception of near-threshold electrical somatosensory stimuli in humans were investigated: subliminal (peripheral) noise (Study I: Iliopoulos et al. 2014), subliminal pulsed stimulation (Study II: Iliopoulos et al. 2020) and interoceptive (cardiac) signals (Study III: Al et al. 2020).

Study I) Peripheral noise: Subliminal (imperceptible) noise enhances detection performance via stochastic resonance (Iliopoulos et al. 2014)

Noise is a source of randomness constantly present during the different processing levels of a stimulus and can stem peripherally, before the central integration of the sensory input of a stimulus, but it is also continuously present in the cortex as a result of non-task relevant and/or spontaneous background synaptic activity. Thus, noise is omnipresent on all hierarchical levels of the nervous system, during all the different phases of stimulus processing. This random interference of the afferent task-related information with noise at various processing levels is one of the reasons why an identical stimulus is sometimes perceived consciously and sometimes not. Neurons are also typically characterized by a high degree of variability in their firing activity leading to stochastic fluctuations. As a result of this overall non-deterministic behavior of the nervous system, the neural response will still vary each time we stimulate, even if the stimulus is completely identical as to its intensity, duration and location (Lu and Dosher

1999; Neri 2010). Along these lines, noise was initially regarded as an enforcer of unpredictability and performance fluctuation, a rather detrimental role when trying to establish a link between brain activity and psychophysical performance. This notion was later challenged by numerous models which interpreted noise not as a variable harmful to stimulus processing but as a crucial computational component in decision making (for review see Deco and Romo, 2008). Moreover, and beyond the role of noise as a factor of instability in behavior, these models reveal that the neuronal fluctuations lead to probabilistic behavior in decision making. This allows our brain function to vary performance along the dimension of time (within and between trials) and adapt dynamically to the probabilistic variance of external events (stochastic/probabilistic excitability) occurring in the natural environment.

We are often faced with the common task of focusing on certain things while at the same time attempting to ignore the overwhelming flow of task-irrelevant information entering our senses. When we do this, we are making a determination as to what information is important to sense and what is noise, we are basically detecting a signal. In general, noise is harmful for signal detection. This is why we are often annoyed by a noisy environment while trying to have a conversation (e.g. busy street full of traffic/ room full of people talking loud simultaneously), especially if the voice intensity is low. For this reason, noise was traditionally considered to be detrimental or a factor of nuisance for retrieving important information out of a signal. The most commonly used indicator of the quality of a signal, the signal to noise ratio (SNR), evidently decreases when noise increases. Interestingly, there are instances where detection of a signal actually improves until noise is increased up to a certain level and if noise continuous to increase over this level, signal detection declines again. This quadratic relationship (described by a resonance/peak-shaped curve)between noise and signal determines an optimal noise intensity for which signal detection is also optimal, i.e. the nervous system reaches a state of resonance where information processing is most efficient. This outlines the phenomenon of stochastic resonance (SR). “Stochastic resonance is a mechanism by which a system embedded in a noisy environment acquires an enhanced sensitivity towards small external time-dependent forcings/excitations” (see review of Moss et al. 2004). It highlights the possibility that noise, may actually benefit the detection of a signal. The probabilistic excitability of such “stochastic” systems allows them to reach a stable, optimal state for signal detection. A crucial aspect of SR is the particular relationship between noise intensity and signal detection which is described by an inverse U-shaped curve. Over the last thirty years numerous studies revealed SR effects on different modules of the human brain: the auditory (Morse and Evans 1996; Ward et al. 2001; Zeng et al. 2000), visual (Kitajo et al. 2003; Piana et al. 2000; Simonotto et al. 1999; Ward et al. 2001), and tactile sensory (somatosensory) system (Collins et al. 1997; Richardson et al. 1998; Priplata et al. 2002, 2003;). In order to test a possible enhancement on detection, many of the early somatosensory paradigms combined vibrotactile with electrical

stimulation. For example Richardson et al. reported that a tactile stimulus accompanied by a randomly varying electrical signal resulted in SR detection enhancement (Richardson et al. 1998). In this context, external noise of optimal level has been repeatedly shown to improve tactile task efficiency (for review see Beceren et al. 2013). Such findings have further contributed in the development of fine-movement tuning clinical applications such as surgical grasping (Sueda et al. 2013; Sawada et al. 2015) and postural/balance improvement (Magalhães and Kohn 2011). Moreover, and beyond the modal specificity of the peripheral stimuli, SR was frequently shown to occur during crossmodal/multisensory processing (Lugo et al. 2008; for review see Liu et al. 2010; van der Groen and Wenderoth 2016). From peripheral stimulation to crossmodal integration, the occurrence of SR at different hierarchical levels of information processing favors the hypothesis that the human CNS has evolved the capacity to dynamically adapt in noisy environments by actually benefiting of a specific, "optimal" amount of noise to best serve the processing of sensory information in a constantly fluctuating environment.

One of our own early findings that shifted our attention to the importance of the role of noise in the processing of a stimulus was presented by Blankenburg et al. (2003). This study showed that electrical finger nerve stimulation with continuous 7 Hz subthreshold stimulation was accompanied by (i) a focal negative fMRI-BOLD signal change in contralateral primary somatosensory cortex (S1) and (ii) decreased perception of near-threshold target stimuli when embedded in the subthreshold pulse train at a target pulse delay of 30 ms (Blankenburg et al. 2003; Taskin et al. 2008). Both BOLD reduction as well as perceptual impediment due to the subthreshold pulse train stimulation were interpreted to rely on intracortical synaptic feed-forward inhibition while the net cortical deactivation was presumed to be underlaid by "an automatic, non-conscious noise-suppression mechanism, arising at a low level of sensory processing, and acting to reserve cortical capacity and conscious awareness for task-significant stimuli" (Blankenburg et al. 2003). This "gatekeeper" function selects which inputs would be further processed in the cortex. According to this model, thalamocortical inhibition closes the gate for processing weak stimuli that are not followed by additional afferent input allowing only strong or long-lasting afferent signals to be processed in the cortex and potentially become consciously perceived. Feed-forward inhibition introduces an early classification criterion by discriminating stimuli as signals or noise thus offering a mechanism to keep the cortex unexposed to harmful amounts of subliminal noise. The question remained as to whether this noise stems peripherally or resides only in the CNS. According to the proposed model, "weak subliminal stimuli are classified as noise and the system then raises the detection threshold to exclude such noise stimuli as being non- task-relevant (task unrelated)" (Blankenburg et al. 2003). This claim raised new questions about the site of the possible interaction between noise and external sensory input (peripheral and/or CNS) and brought forth the idea of manipulating

this cortical subliminal noise via external, subliminal electrical noise, thus modulating the system's threshold and the processing outcome in a non-conscious manner, i.e., if lowering the threshold protects the cortex from noise, would introducing noise peripherally inversely mediate a change on threshold? The feed-forward inhibition model sufficiently explains decreased detection performance as a result of noisy input but how is enhanced detection or fine tuning achieved in real life-noisy conditions? Is noise always harmful to detection? What is the relationship between electrical noise signal (ENS) input and behavioral performance? These are the main questions that motivated behavioral study I. As a first, trivial step towards disclosing specific processing mechanisms that underlie detection modulation due to ENS, this study was restricted to just psychophysical assessments. In detail, the objectives and specific hypothesis of this study were as follows:

Effects of subliminal noise stimulation on detection:

1) Can the detection of electrical pulses (target stimuli) be modulated or even enhanced by introducing a particular level of subliminal electrical noise? Is this enhancement driven by SR? In which circumstances does this occur?
2) Do ENS and targets interfere within the CNS or is it merely a peripheral effect (i.e. within the afferent nerve)?
   Which are the optimal properties of the noise signal to apply (power spectrum distribution, sample frequency, filtering, and other temporal aspects) in relation to the targets? What is the relation between subliminal noise signal stimulation and the sensitivity of the subjects?

Study II) Effects of repetitive versus transient subliminal stimulation on oscillatory activity and detection performance (Iliopoulos et al. 2020)

Somatosensory stimulation modulates cortical oscillatory dynamics and behavioral performance (Blankenburg et al. 2003; for review see Kouider and Dehaene 2007; Del Cul et al. 2009; for review see van Gaal et al. 2012; Nierhaus et al. 2015; Baumgarten et al. 2017; Forschack et al. 2017) while the neural reaction to external stimuli and its access to consciousness depends not only on the stimulus but also on the cortical state (van Dijk et al. 2008; Blankenburg et al. 2003; Weisz et al. 2014). To investigate the mechanisms that lead to conscious awareness, previous research regarded behavior as a result of interference between cortical oscillations and external stimulation. Several studies report that cortical oscillatory activity is a major factor to influence the processing of sensory stimuli (Ergenoglu et al. 2004; Babiloni et al. 2006; Hanslmayr et al. 2007; van Dijk et al. 2008; Schubert et al. 2009; Baumgarten et al. 2016; Benwell et al. 2017; Stephani et al. 2021; Zhou et al. 2021). Given that oscillatory activity itself is influenced/shaped by incoming external stimuli (Miller et al. 2007;

Mazaheri et al. 2009; Sauseng et al. 2009; Herrmann et al. 2016; Li et al. 2019; Lin et al. 2021), the modulation of neural oscillations has often been considered a potential mediator of the behavioral effects elicited by external stimuli. In this framework, investigating the role of the alpha rhythm in the somatosensory system (sensorimotor alpha) has been in the spotlight for at least three decades. Most previous studies have established the notion that alpha rhythm strength is inversely related to cortical excitability (Jensen and Mazaheri 2010; Jensen et al. 2012; Klimesch et al. 2007; Romei et al. 2010) and also inversely related to detection performance of near-threshold somatosensory stimuli (Baumgarten et al. 2016; Jones et al. 2009). However, as stated in Craddock et al. (2017) "several other studies have reported a quadratic relationship between alpha and performance and have associated intermediate power levels to improved hit rates (Linkenkaer-Hansen et al. 2004; Weisz et al. 2014; Zhang and Ding 2010; Forschack et al. 2017)".

In a similar context, as a general basic approach in most of the previous studies of our group, the focus was on how external stimulation influences neural correlates and/or psychophysical performance. Along the lines of the studies mentioned above, previous findings of our own group have shown that subliminal pulses induce an increase in Mu (sensorimotor alpha) rhythm (Nierhaus et al. 2015; Forschack et al. 2017). In contrast to Mu-desynchronization following suprathreshold stimuli, increases in sensorimotor alpha rhythm were typically linked to a "deactivated" state of the somatosensory system. On the other hand, it was also shown that continuous pulsed stimulation at 7 Hz (pulse trains) inhibited the somatosensory system (Blankenburg et al. 2003; Taskin et al. 2008). These findings together led me and my colleagues to postulate that changes in sensorimotor alpha synchrony induced by subliminal stimulation can mediate (and provide the underlying cortical mechanism) of a behavioral outcome. Up to this point, though our findings clearly showed that both continuous pulsed stimulation (pulse trains delivered in long blocks) and single pulse stimulation modulate brain function, their effects have only been tested in different experimental designs (block versus event-related design) and therefore could not be compared, nor further assumptions on the role of spontaneous oscillations on detection performance could have been made so far. Study II aimed to reconcile the role of alpha (Mu) rhythm by contrasting detection performance of subliminal electrical finger stimulation – presented as single pulses or as brief (1 s) 7 Hz pulse trains in a common, event-related design. By systematically varying the respective latency between subthreshold stimulation and targets, and by implementing both EEG and psychophysics, we hypothesized that the increase in Mu-rhythm is the link between subliminal pulse stimulation and inhibition of the somatosensory system.

In particular, the objectives/hypotheses of this study are:

Effects of imperceptible single pulse versus pulse train stimulation on oscillatory activity and detection:

1) Are changes in sensorimotor alpha synchrony following imperceptible stimulation related to a psychophysical effect?
2) What is the impact of each type of stimulus on detection performance? Can we attribute functional inhibition to both single and train targets?
3) How does each type of stimulus affect ongoing cortical oscillatory activity? Do imperceptible trains also increase mu-alpha synchronization as single pulses were previously shown to do (Nierhaus et al. 2015)? How is cortical processing of ongoing stimuli affected by previous stimuli?

Study III) Cardioencephalic interactions modulate somatosensory perception and evoked potentials (Al et al. 2020)

As discussed above, the neural response to external stimuli depends on the state of the brain (Arieli et al. 1996; van Dijk et al. 2008; Blankenburg et al. 2003; Weisz et al. 2014; Gelbard-Sagiv et al. 2018). Furthermore, the cortical state is known to be significantly influenced by signals stemming from internal organs, particularly when compared to very weak external stimuli. Interoceptive afferent signals that stem from autonomic organs, such as the heart, have been frequently investigated as potential modulators of conscious perception: Various studies report that perception (Sandman et al. 1977; Motyka et al. 2019) and EEG correlates (Walker and Sandman 1982; Sandman 1984) of visual and acoustic stimuli depend on the phase of the cardiac cycle. Furthermore, another study showed that additionally, the heartbeat evoked potential (HEP) also affects conscious detection of visual stimuli (Park et al. 2014). These findings together indicate that cardiac interoceptive signals possibly affect conscious perception of external stimuli, nevertheless, fundamental questions regarding the interaction of the heart with ongoing oscillatory activity and external somatosensory stimulation remain open. This motivated study III which aimed to investigate the impact of cardiac activity on somatosensory perception.

By implementing signal detection theory analysis, EEG and electrocardiography (ECG), we postulated that the cardiac phase and the HEP shape somatosensory detection and cortical processing. As a secondary hypothesis, we tested whether pre-stimulus sensorimotor alpha might also mediate the influence of the cardiac phase on perception of target stimuli. Apart from measuring detection performance, the task additionally tested the subjects' ability to localize stimuli delivered on different fingers.

As discussed above, this design allowed assessment of a potential internal (cardio-cortical) modulation effect rising from cardiac activity, i.e., the effect of the HEP on detection performance. This interoceptive cardio-cortical modulation can be also regarded as a type of additional internal (not inherit in the external stimulus) source of performance fluctuation. As shown in a previous study, heartbeat-related activity modulates the spiking pattern of afferent (peripheral) neurons through baroreceptor pressure fluctuations (Macefield 2003). This pulse-synchronous - and thus predictable - event might be responsible of introducing a central (top-down) pulse-associated noise-suppression function which decreases the ability of the cortex to differentiate between external sensory input (especially of weak intensity) and noise. This study additionally aimed to complement on the role of "internal noise" (in this case the term "noise" refers to pulse-synchronous, non-task related, cortical activity rising from the HEP and has no relation to peripheral noise which stems externally) as a tuning parameter of a noise-"gatekeeper" function. Considering the previously discussed, well-known modulating effects of external noise on perception, this finding (Macefield 2003) motivated a first complementary assessment of a potential "internal noise" effect rising from cardiac activity. From this perspective, the pulse wave-associated suppression mechanism present in the cortex whose main function appears to be the suppression of the heartbeat, might also lead to the suppression of weak external stimuli (Macefield 2003) and modulate performance. The specific objectives that motivated this study are:

Heart-brain interactions:

1) What is the influence of heartbeat-related activity (neural as well as hemodynamic) on conscious perception?
2) Does detection and localization performance change when we deliver the same stimulus in different time points of the cardiac cycle?
3) How are "sensitivity" and "criterion" (in the nomenclature according to signal detection theory) affected by the cardiac cycle?
4) Does the amplitude of the heart evoked potential (HEP) affect psychophysical performance? Are the stimuli evoked potentials modulated by the HEP? Does sensorimotor alpha activity (Mu) mediate the effect of the cardiac cycle on task performance?

2. Methods

In this section, an overview of the implemented methods is provided. The complete information describing the implemented methods in each study is provided in the “methods” section of the respective publications as cited subsequently.

Studies II and III combine both psychophysical and EEG recordings while study I contains only psychophysical measurements. The EEG setups in studies II and III were similar except for the number/location of the electrodes. Throughout this section, the common methodology will be described briefly while emphasis will be given on the technical differences of the methods applied in each study.

2.1 Subjects and experimental design

All studies were performed on healthy subjects without any history of neurological or psychiatric disorder aged between 18-40 years. All participants volunteered and were compensated. Before each measurement, subjects were informed accordingly and gave written consent in compliance to the Declaration of Helsinki. All studies had been approved by the corresponding local ethics committee of the Charité – Universitätsmedizin (study I) and Leipzig University (studies II, III) before initiating the measurements.

Study I

We were interested in testing the interaction between noise and target stimuli in respect to detection performance. To investigate the conditions under which this interaction modulates detection we systematically varied the temporal pattern of both the target (types of implemented targets: single short pulses, single long pulses and pulse trains) and the noise signal (slow noise, fast noise and sinusoidal noise). Additionally, to investigate whether this interaction occurs centrally or peripherally we delivered the stimulus in two different locations (both signals delivered either on the same or adjacent finger). Participants sat in a comfortable chair in front of an instruction monitor and received near-threshold target pulses of different duration on the left index finger along with concomitant subliminal noise stimulation of different temporal pattern on the same or adjacent (digit 3) finger in different experiments. Five psychophysical experiments where performed:

Exp 1: Single short pulse-targets vs single short pulse-targets with slow noise at the same finger.

Exp 2: Single short pulse-targets vs single short pulse-targets with sinusoidal noise at the same finger.
Exp 3: Singe short pulse-targets vs single short pulse-targets with slow noise at the same or adjacent finger.
Exp 4: Pulse train targets vs pulse trains targets with slow noise at the same or adjacent finger.
Exp 5: Long targets vs long targets with fast noise at the same or adjacent finger.

In the first four experimental paradigms, participants were instructed to stay alert and respond via a button as soon as they would perceive a target signal. In experiment 5 they were asked to always answer whether a trial contained a stimulus or not in a two alternative forced-choice task (2AFC). Inexperienced participants were submitted to brief training and prior to each recorded block the somatosensory detection threshold of each participant was defined in two-decimal precision. A total of 54 participants were recruited for this study.

Study II

In a similar setup as in study I, participants received near-threshold target pulses on their left index finger. In the EEG paradigm participants received either a single imperceptible pulse or an imperceptible pulse train on absence of target stimuli. To assure awareness during this passive EEG recording, participants were instructed to report counting of strong scarce supraliminal targets only after the recording of each block. To measure psychophysical performance, an imperceptible single pulse (three experiments) or a pulse train (three experiments) was delivered in combination with a near-threshold TPs at three different time offsets (30 ms, 60 ms, and 180 ms). Each condition corresponding to a different time delay was then examined in contrast to the control condition (i.e., trials containing only target stimuli) in six different experiments. In two of the pulse train experiments, the TP was introduced right after the fifth (imperceptible) pulse of the train (i.e., “embedded” in the train) while in a separate experiment the target was presented 180 ms after pulse train offset. The same conditions were tested for single pulses in the resting three experiments. Participants were instructed to remain alert and respond using the right index finger via a button as soon as they would perceive a target signal. Overall, one EEG and six psychophysical experiments were performed on 158 participants in total (40 participants in the EEG experiment).

Study III

As in study I, participants sat in front of an instruction monitor and received near threshold target pulses either on the index (d2) or middle (d3) finger of the left hand. To obtain measures of sensitivity, in this study we applied a 2AFC paradigm containing dummy/null trials according to signal detection theory. To increase statistical power per stimulation condition, participants

would receive only one intensity of near-threshold (NT) target stimuli at 50% threshold value. The stimulation intensity was adapted after each measurement block according to the detection curve of the subject. The participants were instructed to first detect and then localize a target stimulus via motor response (button press using the right hand). For undetected stimuli they were instructed to try and nevertheless guess where the target was delivered.

2.2 Electrical stimulation

As reported analytically in Iliopoulos et al. 2014, “electrical finger nerve stimulation was performed with a bipolar constant-current stimulator (DS5; Digitimer, Welwyn Garden City, Hertfordshire, United Kingdom) and steel wire ring electrodes”. All signal waveforms were created using LabVIEW (Bitter et al. 2006) and MATLAB (releases 2011, 2014b, 2019b, The MathWorks, Inc., Natick, Massachusetts, United States) via the open-source toolbox PSYCHTOOLBOX (releases 3.0.11 and 3.0.14) and generated as analog voltage signals through a National Instruments data acquisition card (National Instruments, NI-usb-6229).

2.3 Data acquisition

Electroencephalography

In study II, we recorded cortical signals using 32 electrodes placed on the scalp according to the international 10–20 system, with broadly used EEG acquisition systems (actiCap, Brain Products GmbH, Gilching, Germany). Electrode FPz served as the reference while the electrode used as ground was placed on the sternum.
In study III, we recorded cortical signals using 62 electrodes placed on the scalp according to the international 10–10 system with broadly used EEG acquisition systems (actiCap, Brain Products GmbH, Gilching, Germany). Again, the ground electrode was placed at the sternum while electrode FCz was the reference. An ECG electrode was additionally placed along the midaxillary line on the lateral left side of the thorax to record heart activity.

Psychophysics

All voltage signals were recorded simultaneously and in parallel as analog inputs of a DAQ card (National Instruments, NI-usb-6229). The threshold assessment was performed online during the experiment while all further analyses were performed offline based on these recordings.

2.4 Data analysis

All psychophysical data were analyzed by implementing self-compiled scripts in MATLAB.

Electroencephalographic recordings were band-pass-filtered to eliminate low frequency drifts and high-frequency noise as explained in detail in the methods section of each publication. EEG preprocessing and data analysis was principally carried out using self-compiled coding in MATLAB, the open-source MATLAB toolbox EEGLAB (Delorme and Makeig, 2004) and the open-source MATLAB toolbox FIELDTRIP (Oostenveld et al. 2011).

Study II

By following an offline segmentation as well as wavelet transformation analysis, we examined the neural correlates of repetitive versus single stimulation and compared these across the different stimulation conditions. For cluster analysis and statistical comparison, we implemented non-parametrical algorithms mostly adapted/modified from the FIELDTRIP toolbox.

Study III

Detection and localization efficiency were assessed during the cardiac cycle using circular and binary analyses (Kubios HRV Analysis Software 2.2, The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland).

3. Results

Study I

Our findings demonstrate that subliminal electrical noise stimulation (ENS) can significantly enhance conscious perception of near threshold pulses. Subliminal noise enhances detection performance in a rather selective manner: When ENS and targets are applied on the same finger the most plausible mechanism of interaction seems to be mere peripheral direct current addition. When we stimulate using either pulse trains or long single pulses as targets (in contrast to single pulses), detection performance is further enhanced. The same occurs when we apply fast-, instead of slow noise. Moreover, the fast noise signal is shown to enhance detection even when applied on the adjacent finger. This is a robust indication that the interaction between ENS and targets occurs in the CNS. Most importantly, as shown below in fig. 1 (published as fig. 12B in Iliopoulos et al. 2014), we demonstrate that the relation between subliminal ENS intensity exhibits characteristic stochastic resonance behavior as revealed clearly by the classic stochastic resonance inverse U-shape curve.

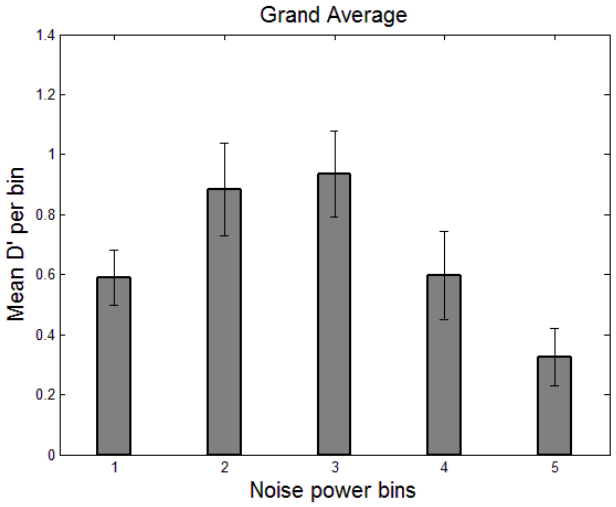

Fig.1 (published as fig. 12B in Iliopoulos et al. 2014). The relationship between subliminal ENS and sensitivity of detection is quadratic and it resembles the classic stochastic resonance signature-curve.

Study II

As our previous findings suggested, subliminal single pulses are followed by a characteristic transitory increase of mu/alpha synchronization (fig. 2). In contrast to this finding, we demonstrated for the first time that subliminal pulse train stimulation was followed by a long pattern of mu-alpha desynchronization. As stated in Iliopoulos et al. 2020, “interestingly, the modulatory effect of subliminal train stimulation even exceeded the period of desynchronization, since mu-alpha activity of subsequent trials was still affected (e.g., mu-alpha synchronization was absent when the single pulse followed a previous train stimulation)”. Behaviorally, subliminal train stimulation decreased conscious awareness of target pulses at all tested delays whereas single subthreshold pulses improved target detection (at an offset of 60 ms) or did not modulate detection significantly (at offsets of 30 and 180 ms, respectively). Our findings support the conclusion that a single pulse enhances synchrony of sensorimotor alpha. Assuming an inhibitory effect of Mu alpha, the facilitation of detection at 60 ms delay might be due to a decrease of central noise and the associated facilitation only for a certain time window. When the pulses are rapidly repeated (pulse trains), however, the inhibitory effect might accumulate, loose its temporal specificity i.e., become dominant for the entire time period leading to a functional inhibition at all delays.

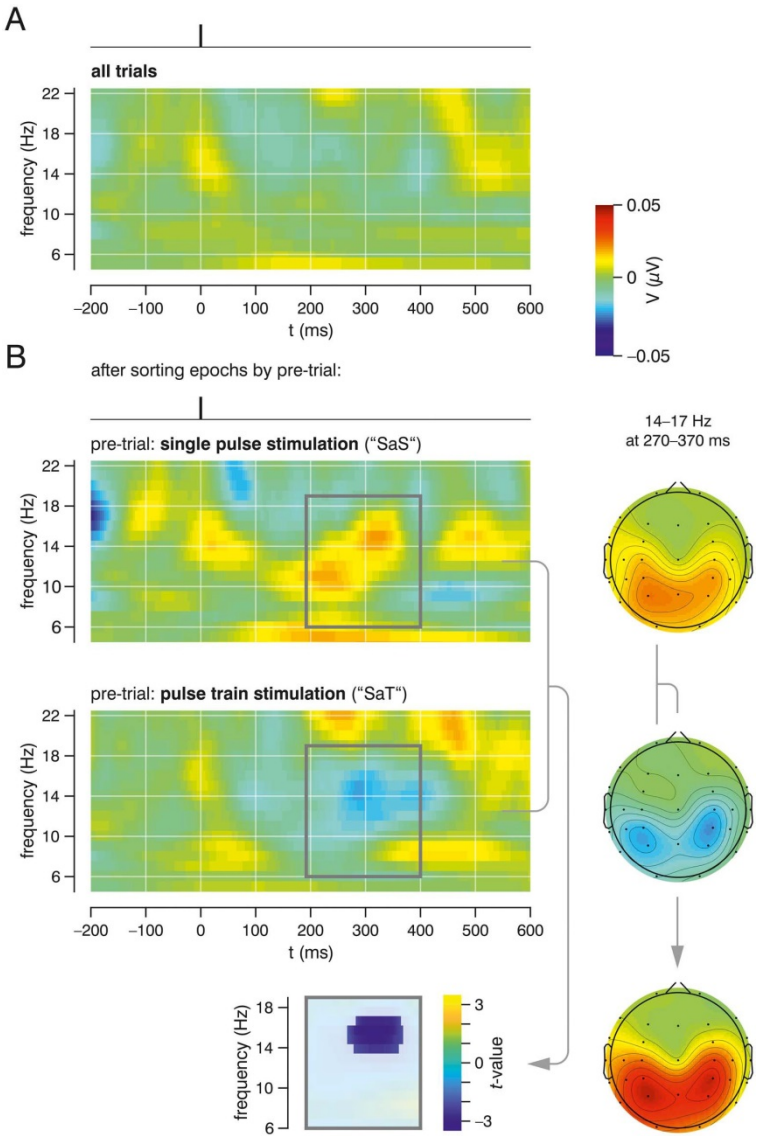

Fig. 2 (published as fig. 3 in Iliopoulos et al. 2020). Effect of subliminal single pulse stimulation. (*A*) Averaging all trials regardless of past trial history does not reveal any significant modulation in the EEG frequency bandwidth in display. (*B*) If we control for preceding stimuli by sorting trials according to the previous trial condition: "single pulse after single pulse" (SaS, upper panel) and "single pulse after pulse train" (SaT, lower panel) we reveal a significant cluster at ~200 ms post-stimulus.

Study III

We show that the detection rate of near-threshold stimuli delivered during diastole was higher than during systole (fig. 3). Furthermore, a weaker HEP was associated with a stronger detection, i.e., there was an inverse relationship. The two mechanisms (systole/diastole and HEP) also affected the parameters of signal detection theory (sensitivity, criterion) differently: Interestingly, the cardiac phase significantly changed only sensitivity of the subjects while the HEP had a significant effect only on the decision criterion. Additionally as reported in Al et al. 2020, “the cardiac phase influenced only late components of the SEPs (P300), whereas the effects of HEP amplitude were observed in both early (P50) and late SEP components. While pre-stimulus sensorimotor alpha power also influenced perception and somatosensory processing, its effect was independent of both heart-beat-related effects on conscious perception, that is, sensorimotor alpha power and heartbeat-related events had an additive impact on somatosensory perception.”

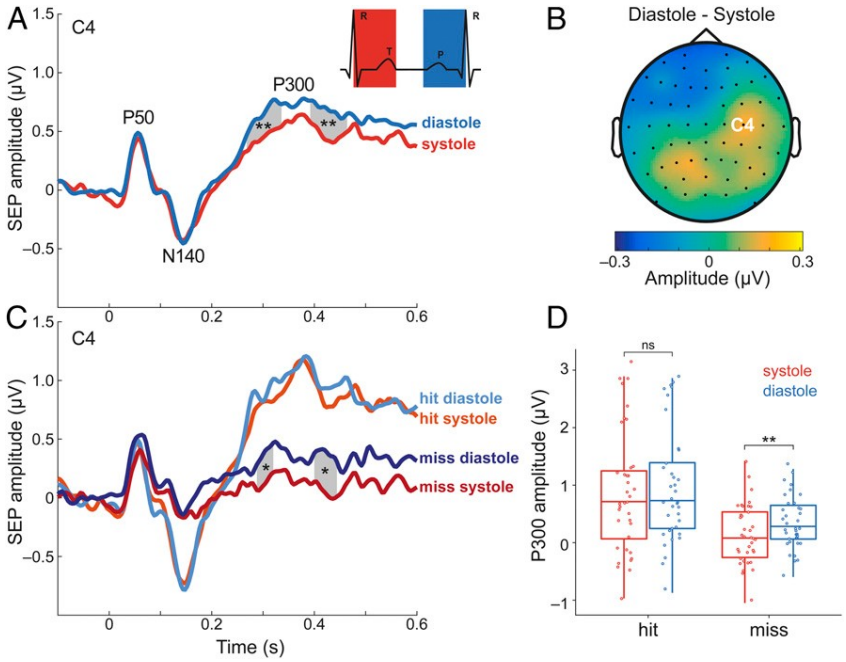

Fig. 3 (published as fig. 3 in Al et al. 2020). The impact of cardiac cycle on somatosensory evoked potentials: Systole and diastole have a differential impact on late SEP components over all as well as over missed trials.

4. Discussion

The three studies demonstrate how peripheral (subliminal noise, single pulses and pulse trains) as well as autonomic factors (heartbeat) can influence perception and the neural response following somatosensory stimulation. Motivated to reconcile previous findings, we hypothesized that non-perceived (subliminal) stimulations can nevertheless modulate task performance without engaging conscious top-down control modulation. This thesis demonstrates that subliminal stimulation indeed can affect the detection of somatosensory stimuli in the CNS. The impact of the applied subliminal modulation is highly versatile and can lead to both enhancement and decline of task performance while the neural response is driven by a time-sensitive interaction between external (concomitant electrophysiological stimulation) and internal signals (ongoing cortical oscillations, HEP and cardiac cycle). While the introduction of this thesis aimed to explain the motivation behind the presented studies, the discussion that follows will address the particular objectives/hypotheses posed earlier, with an emphasis to the specific disclosed key time-characteristics of the interacting signals.

In study I, the detection of target pulses is modulated by introducing a particular level of imperceptible electrical noise and the interaction between the two signals occurs in the CNS. A dynamic temporal dependence between noise and target signals seems to drive this detection modulation. Focusing on the characteristics of this time dependence for the different types of ENS applied in this study, the comparison between the frequency content of the ENS and the frequency content of target pulses was shown to play a crucial role. Respectively, “slow” ENS (frequency content of ENS $\leq$ frequency content of pulses) acts as an external transfer function moderator and enhances detection of targets below the 50% threshold only selectively, in expense to the inhibition of targets above 50%. In this context, “slow” ENS may serve as an arousal moderator. As shown in the 2AFC task, “fast” ENS (frequency content of ENS $\geq$ frequency content of pulses) improves sensitivity (and enhances target detection) when it is applied concomitantly with targets on the same (highest effect) or even on the adjacent finger. The most important finding is that the relation between noise and detection sensitivity for targets of the lowest amplitude is described by the characteristic inverse U-shape SR curve, as shown in fig. 1 (published as fig. 12B in Iliopoulos et al. 2014). This confirms the hypothesis that stochastic resonance effects underlie detection at weak intensities through mechanisms that are operative in the CNS. Simply put, the human CNS can benefit from intermediate levels of noise for which detection of weak, non-predictable signals becomes optimal. In this context, SR is the necessary mechanism that the nervous system evolved to always be able to “tune” to a constantly changing, noisy environment. This allows for example the CNS to protect itself from extreme noise exposure and at the same time to make benefit of the power of mild, ever-present, non-task related signals. SR thus helps us achieve sensory and functional stability and

counterbalance the probabilistic uncertainty that emerges by the ever-ongoing fluctuation of exteroceptive information. As a conclusion, imperceptible ENS can modulate the processing of near threshold stimuli either to improve or attenuate the detection capacity of the subjects by tuning the respective frequency content between targets and ENS signal. Our findings further support the assumption that the human CNS has evolved an internal, functional, intensity- and time-sensitive noise optimal for somatosensory information processing. As we demonstrate, subliminal ENS can serve adaptively on one hand as a fine-tuning detection enhancer that facilitates the access of significant stimuli to consciousness, and/or as a detection attenuator mechanism that most likely acts to protect the cortex from detrimental (as to the cortical processing efficiency) subliminal noise accumulation.

Study II shows that two types of weak imperceptible stimulation (single pulses versus 1 s pulse trains) induce differential effects on perception i.e., brief facilitation versus long-lasting inhibition as well as opposing effects on sensorimotor alpha (mu) rhythm i.e., transient event-related synchronization (ERS) versus long-lasting event-related desynchronization (ERD). We demonstrated that the behavioral relevance of the inhibitory component of the single pulse stimulation (probably indexed by the transient increase of sensorimotor alpha-rhythm) is driven by the progressive accumulation of inhibition in the cortex. In this context, we suggest that the increases on the synchrony of sensorimotor alpha following any subthreshold stimulation do mediate inhibition. For single pulse stimulation, the facilitation of detection at a 60 ms delay might be due to a decrease (inhibition) of central noise leading to a transient facilitation of target stimulus detection only for a certain time window. When the pulses are rapidly repeated (pulse trains), however, the inhibitory effect might accumulate, lose its temporal specificity i.e., become dominant for the entire time period leading to a functional inhibition at all delays.
Moreover, the repetitive stimulation seems to desynchronize the (induced?) sensorimotor alpha. These results suggest that imperceptible subliminal stimuli can form a particularly useful tool for external shaping of oscillatory dynamics and perception since they may induce perceptual effects without cognitive control modulation. Notwithstanding, we show that accumulation of inhibition does not necessarily go hand in hand with mu amplitude increase. We interpret the uncommon, strongly suppressed cortical state, as a result of accumulated inhibition induced externally by the repetitive stimulus in a non-concomitant manner (external 7 Hz is different from the endogenous alpha background rhythm). As a finding of non-functional relevance, the apparent desynchronization is caused by the overlay of different induced effects on the somatosensory cortex. This points to the intriguing possibility that oscillatory dynamics could be potentially shaped also via concomitant (as to the ongoing alpha frequency) external subthreshold stimulation, possibly leading to a cortical state of different synchrony (steady-state somatosensory response). Thus, in contrast to the view that increased alpha facilitates functional inhibition, the current study shows that both low alpha synchrony or even highly

desynchronized alpha activity can accompany a suppressed cortical state while it depicts the key-role of the accumulation of cortical inhibition in time. Apart from providing novel fundamental information regarding the role of alpha on cortical processing, our findings invite future studies to test external oscillatory shaping by implementing a design allowing for direct comparison of behavioral and oscillatory correlates.

Study III demonstrates that detection performance increased during diastole in comparison to systole and also decreased as the preceding HEP increased. In response to the initial hypothesis, we disclosed two plausible mechanisms according to which heart activity afferents modulate conscious perception. According to the first mechanism, increased heart-evoked potentials before stimulation indicate a subsequent time window of decreased (external) somatosensory detection. We attributed this performance decrease to a shift of the bias criterion towards more conservative decisions. Intriguingly, a decrease in criterion went along with increased early and late components of the somatosensory-evoked responses. Secondly, stimulating along different points of the cardiac cycle affected sensitivity but not the decision criterion, which is reflected only in late SEP. In the same vein as above, we suggest that the cardiac-related modulations are due to fluctuations of non-conscious predictive coding. Evidently, the brain constantly monitors and updates cortical representations of afferent information stemming from both exogenous and endogenous sensory input. We claim that the cortical mechanism that mediates the effect of the heart on neural response, is the same mechanism responsible for differentiating internal (originating either from the fingers baroreceptors or directly from the heart) from external signals. In this vein, this mechanism provides a more stable, less “noisy”, more predictable detection function over time by attenuating cardiac activity-related fluctuations that could have been mistakenly perceived as peripheral stimuli. This comes with the expense of some information loss that decreases performance, for example targets that reach the cortex at the same time with an HEP of strong amplitude are mistakenly classified as internal signals. Trivial but also very intriguing, this interpretation depicts the fact that the cortical processing is underlined by a mechanism that processes information in a similar manner regardless whether this originates outside or from within our body. Additionally, the cortex receives and streams information from/to external sensory receptors and internal organs mostly in a parallel manner (internal organs and peripheral sensors seem to have at least one direct, fast, unique pathway to the cortex), thus enabling global (both external and internal) simultaneous cortical access to all afferent information. Any external event (occurring outside our body) is bound to have time- and spatial components. But internal and external events are perceived very differently, so how can the cortex deal with both in a similar manner? How does the brain analyze time and space components related to multidimensional peripheral events? Which part of the code is common for both internal and external events for the cortex?

External events feel quite different than internal events. Phenomenologically, they feel much different more than anything in space. Perhaps a milestone difference comes from the fact that all external sensory input (maybe with the only exception being the receptive fields stemming from the genitals, the only non-duplicated exteroceptive sensory organ in our body) stems from duplicated sensory organs (limbs, eyes, ears, etc.). The cortical illustration of a single external event (in our case a tactile stimulus) is thus always double in brain/internal space (for example contra- and ipsilateral). Moreover the anatomical symmetry of the sensory organs and the proportional symmetry of the corresponding pathways make this information available to the cortex in a synchronous manner via two parallel channels. As a result, we form our perception of the external world always in a dynamic "double source" manner, which offers the ability to make fast and precise space-related comparisons, i.e., we can immediately and easily tell up from down/ left from right, etc. The information corresponding to external events is inserted in our body in a differential manner (left/up is always different to right/down) already partially disentangled in space. This means that if a strong stimulus is delivered to a site as small as a fingers receptive field (like in our paradigms) then this inserted information is already completely disentangled in space when it reaches the cortex. Any strong visual, acoustic, or tactile stimulus will always have this dynamic, "double source" context and the information that corresponds to external events will always carry a, so to say, "double precision" content. So the percept of the exterior world is always based on packages of "dual" information and this offers a simple way to perform direct one-to-one comparisons every moment. Furthermore, by decussating and recombining these two streams (left/right, up/down, etc.) of information, the brain has the ability to maintain information longer and perform more complicated comparisons of states over different time points (current/before/after). In contrast, internal organs are mostly non-duplicated, and the information stemming from them lacks components of space (one exception being proprioception). The important piece of information carried here is mostly related to time, i.e., it is more important/easier for us to feel when a heartbeat took place, we don't often question where did it come from. It seems that the common part of the information describing internal (mostly monodimensional) and external events is the common time components. Most likely to serve the optimal efficiency of task performance in time, the cortex seems mostly engaged on the level where the necessary, essential time-specific comparisons take place. In this framework, the role of the cortex seems to be the disentangling and recombining of the time components of both internal and external events to obey task demands.

As we claim above, there is a mechanism for which cortical coding is the same for afferent information stemming from an internal or an external event. The nervous system seems able to break-down and compare location/space- (periphery, lower CNS) and time-related components

(cortex) of an external event related to a specific task. Equally impressive, our brains are also able to “compose” time- and location- related information regarding our body and express it exteriorly always in a time-synchronous manner. Considering the above, and beyond the role of the agency of an “internal” organ that is closely related to our “own” consciousness, the cortex seems to be a relay site where the corresponding extero- and interoceptive information that flows in and out our body is compared. This information, regardless of origin, is processed in the cortex and organized in such a way that is expressed sequentially out of our body in a synchronous manner. In this vein, and beyond the notion of “owning” consciousness (which erroneously makes us imagine consciousness as something located/bounded within the physical limits of our body/brain and additionally creates the illusion of having conscious control over consciousness), the cortex is the sync-unit between the ever-going flow of information between the interior of our body and the rest of the physical world. Simply put, the cortex enables sync of data between two different streams of information that run in parallel. It allows syncing data flow and communication between the internal and the external domains by generating/offering a common time basis, always prioritizing task performance. In this vein, and beyond the robust computational capacity of the cortex, the cortex offers the necessary continuum between the time in the observatory/natural (exterior) world and internal events. As a conclusion, our findings provide robust proof that cardiac activity is a significant determinant of the cortical response to somatosensory stimuli and its access on consciousness and allow attributing at least a fraction of what was previously considered as random internal noise leading to unpredictable fluctuations, to deterministic autonomic activity.

All three studies published novel findings many of which have been cited by other research groups replicated in pilot studies of our own group in different subsequent experiments. However, producing a generalized model that describes how the three determinants of consciousness (imperceptible noise, imperceptible pulse stimulation, cardiac activity) interact with ongoing oscillations to achieve a behavioral outcome is confounded by the experimental designs. The main limitation to this purpose is that in studies I and II the implemented paradigms do not allow for a direct comparison between neural correlates and behavioral performance, i.e., study I is merely psychophysical (does not assess EEG) while the EEG and psychophysical measurements of study II where recorded in separate sessions (and moreover under different task conditions) and thus the effects cannot be placed with certainty in direct juxtaposition. An additional limitation concerning the role of cardiac activity is introduced by the absence of ECG recordings in studies I and II. Evidently, any future designs investigating externally modulated oscillatory activity in a similar framework should allow for a direct comparison of behavioral and EEG correlates and record ECG activity at the same time (simultaneous recording).

Nevertheless, the findings of the three studies lead to general conclusions and point to a common direction. As a general outcome comment on the integration of the neural response to a stimulus and its access to consciousness, this dissertation reaffirms the high degree of time-precision and specificity of the presented effects depending on the time-content of the interacting signals. A characteristic finding disclosing the high time-precision of the effects underlying detection is shown in study II, where delivering a target with a post-stimulus offset of 60 ms already has a different impact on psychophysical performance than a 30 ms offset. In study I, the fast ENS signal also has a differential effect compared to slow ENS while the effect changes for pulse train targets. Following the above discussion on how the cortex offers a common time basis for internal and external events, these findings shift attention again on how the brain keeps track of time and how endogenous timing brain processes disentangle from sensory-driven processes (Klimesch et al. 2007; Jacobs et al. 2007; for review see Paton and Buonomano 2018). As a general remark along these lines, various findings attribute the ability of the cortex for high temporal precision to the strength of oscillatory coupling (Jacobs et al. 2007; Jensen and Mazaheri 2010), thus correlating the time-precision of behavioral performance to the variance of neural computations (Grabot et al. 2019). Cortical processing appears to be operating adaptively and in a versatile, flexible manner to most efficiently serve task efficiency, even during the presence of conversely distinct cortical states (ERD/ERS), as shown in study II. This indicates that the different integration and processing levels of a stimulus are organized in each case adaptively to best serve the specific needs of task execution. In this vein, it becomes obvious that the hierarchical organization of the different levels of stimulus-processing can only be investigated in respect to specific task-performance, i.e., the access to consciousness depends on the implemented task itself and does not make sense to refer to accessing consciousness on absence of a specific task. Optimal task efficiency (in time) appears to drive the organization of the processing capacities of the brain, i.e., even for very distinct tasks implementing the same stimulus, the brain appears able to allocate necessary resources and re-direct the processing stream to always perform precisely as instructed, in the most efficient manner in time: able to respond to incoming sensory input as fast as possible while concurrently maintaining synchrony between the different levels of processing. In other words the organization of the nervous system across all the different space-time scales from the cellular to the macroscopic anatomical and electrophysiological levels allows it to generate processing cycles of different time durations that still fit harmonically with one another to hierarchically serve (express outcome in a synchronous manner) the external (task) demands. The capacity of the system to process information in different time scales but still be able to integrate it and exteriorize it sequentially in a synchronous manner assures that the system is constantly task-responsive to new stimuli while able to continuously monitor parallel internal processes at the same time.

In this context, and beyond the use of the term “synchrony” redundant to describe the cortical state (oscillatory resonance of neurons), external stimulation, cortical oscillations, and also cardiac signals, adjust their functions over time and hierarchically organize the central integration and processing of a stimulus in a “synchronous” (in respect to their functions) manner. Moreover, the cyclic, periodical aspect of both the cardiac activity and cortical oscillations suggests a possible optimal/synchronized heart-brain interaction state that enhances the neural and/or behavioral response to external stimuli. Furthermore, findings showing that perception is achieved in discreet cycles (Baumgarten et al. 2017) enforce the notion that modulation of performance occurs rhythmically and selectively over specific time windows. Along these lines, study II discloses inquisitive/challenging findings (see finding of increased detection at 60 ms but not at 30 ms, study II). Regardless whether the extent of each perceptual cycle is measured at the cellular (decay of inhibition) or cortical level, our data suggest that the rhythmical modulation of performance might be driven by the imperceptible external stimuli in terms of entrainment (synchronization of neural responses to an external stimulus): In fig. 4A of Iliopoulos et al. 2020, there seems to be a sustained increase of synchrony at 7 Hz, which might indicate the emergence of a subliminal somatosensory steady-state evoked potential (SSSEP). This potentially entraining effect is even stronger when the train is presented after a single pulse (fig. 4B, Iliopoulos et al. 2020). Beyond the specific future repercussions of each study as explained in detail in each publication, and as a first priority in our quest to disentangle the role of the cortical state in the processing of external stimuli, we invite future studies to first test for occurrence of stimulus-driven imperceptible SSSEP (leading to a SSSEP on absence of conscious control) as a fundamental mechanism that can allow to contrast/compare and disentangle behavioral and EEG correlates in response to near-threshold target stimulation. Since conscious top-down monitoring is often considered a mediator of the (cognitive) processing of a stimulus itself, imperceptible stimulation provides the additional advantage of avoiding top-down conscious control that might further entangle with the stimulus processing. To the best of our current knowledge, there is so far no report of a subliminal (induced by imperceptible stimuli) somatosensory steady state. If our hypothesis is confirmed, this clearly proves that the pulse train is processed in a non-conscious manner. As frequently reported, this is well in line with sensorimotor alpha power decreasing, but raises new questions regarding the accompanying behavioral costs. After all, could it be that post-stimulus sensorimotor alpha does not indicate functional inhibition at all? Does sensorimotor alpha power also decrease after a consciously perceivable 7 Hz stimulation and is this decrease accompanied by behavioral costs? These emerging questions can be easily tested by implementing a paradigm containing paired sub-/supra- threshold trains and a single near-threshold target pulse delivered after 180 ms (latency of the strongest effect, study II).

In summary, this thesis investigated three factors that modulate perception of near-threshold somatosensory stimuli in humans: peripheral noise, subliminal single pulse and pulse trains, and heartbeat-related phenomena. The findings presented in this thesis demonstrate that non-conscious/imperceptible stimulation can significantly affect the detection of ongoing (during a block of ENS), embedded (within a pulse train) and subsequent near-threshold target stimuli applied on the same (studies I, II and III) as well as on adjacent fingers (studies I and III). In a systematic attempt to reconcile previous findings and to contribute to the existing models concerning the access of an external stimulus to consciousness, we generated our experimental designs by systematically manipulating key time-features of the imperceptible stimuli, under the general hypothesis that non-perceived signals can nevertheless modulate somatosensory performance of healthy subjects. As we clearly show in the presented studies, the impact of imperceptible stimulation on brain function depends on the characteristic temporal features of the interacting signals in a highly specific and time-precise manner. By tuning their respective temporal content, we show that all external (imperceptible noise, single pulses and pulse trains), cortical (ongoing cortical oscillations) as well as autonomic signals (cardiac activity) decisively influence behavior in different, even opposing directions, thus offering the prospect for flexible and versatile non-conscious shaping of the brain function in different directions.

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Statuatory declaration

I, Foivos Iliopoulos, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “unconscious modulators of somatosensory perception” / “unbewusste modulatoren der somatosensorischen wahrnehmung”, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.

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Date Signature

Declaration of contribution to the publications

Foivos Iliopoulos contributed the following to the below listed publications:

Publication 1: **Iliopoulos F**, Nierhaus T, Villringer A (2015) Electrical noise modulates perception of electrical pulses in humans: sensation enhancement via stochastic resonance. J Neurophysiol; 111(6):1238-1248.

- Contribution: Foivos Iliopoulos conceived the paradigm and designed the experimental protocol (software and hardware setting and synchronization in labview and matlab) for this electrophysiological study, personally performed all measurements and recordings, processed the acquired data and performed the statistical analysis as well as data visualization. All plotting and editing of all figures was perfrormed by himself. He also interpreted the results, wrote all (first and subsequent) drafts of the manuscript and coordinated the journal submission process.

Publication 2: **Iliopoulos F**, Taskin B, Villringer A, Nierhaus T (2020) Imperceptible somatosensory single pulse and pulse train stimulation oppositely modulate mu rhythm activity and perceptual performance. Cerebral Cortex. 30(12):6284-6295.

- Contribution: Foivos Iliopoulos conceived the paradigm and designed the experimental protocol for the following experiments: A2, A3, B2, B3 (see fig.1 of publication 2), for which he personally performed all measurements and recordings, processed the acquired data and performed the statistical analysis as well as data visualization (plotting). Additionally he performed segmentation, time-frequency analysis and plotting of the electroencephalographic data. Figures 1 and 5 were prepared by himself while all authors collaborated for the final edit of figures 2, 3 and 4. The challenging interpretation of the results was performed in collaboration with the rest of the authors. Additionally he wrote all (first and subsequent) drafts of the manuscript and coordinated the journal submission process.

Publication 3: Al E, **Iliopoulos F**, Forschack N, Nierhaus T, Grund M, Motyka P, Gaebler M, Nikulin VV, Villringer A (2020) Heart-brain interactions shape somatosensory perception and evoked potentials. Proc Natl Acad Sci U S A. 117(19):10575-10584.

- Contribution: Fivos Iliopoulos conceived the paradigm and designed the experimental protocol together with Esra Al and Prof. Dr. Arno Villringer (specifically he prepared the code of the experimental protocol entirely himself and contributed posterior software and hardware modifications and synchronization through “Matlab”) for this combined EEG-ECG study which followed previous pilot studies investigating the phenomenon of ‘numb touch’, the somatosensory analog of ‘blindsight’. while participants were

measured in equal contribution with Esra Al. He processed acquired data and performed somatosensory evoked potential analysis as well as data visualization. Specifically, he prepared the scheme in fig. 1 while all other figures and tables were prepared by Esra Al.

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Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

Print versions of the selected publications

Publication 1

Iliopoulos F, Nierhaus T, Villringer A. Electrical noise modulates perception of electrical pulses in humans: sensation enhancement via stochastic resonance. J Neurophysiol, 2015; 111(6):1238-1248
https://doi.org/10.1152/jn.00392.2013

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Extract from the Journal Summary List (Isi Web of KnowledgeSM):

Journal Data Filtered By: **Selected JCR Year: 2011** Selected Editions: SCIE;SSCI
Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WOS

Gesamtanzahl: 244 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
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2	NEURON	64,092	14.736	0.227502
3	BRAIN RESEARCH	59,237	2.728	0.093563
4	NEUROIMAGE	50,569	5.895	0.153562
5	JOURNAL OF PHYSIOLOGY-LONDON	46,154	4.881	0.082698
6	JOURNAL OF NEUROPHYSIOLOGY	43,413	3.316	0.090699
7	NEUROSCIENCE	40,083	3.380	0.091765
8	NATURE NEUROSCIENCE	39,636	15.531	0.159634
9	JOURNAL OF NEUROCHEMISTRY	38,731	4.061	0.081125
10	BRAIN	38,614	9.457	0.099644
11	JOURNAL OF COMPARATIVE NEUROLOGY	35,443	3.808	0.046461
12	BIOLOGICAL PSYCHIATRY	34,481	8.283	0.093875
13	ANNALS OF NEUROLOGY	31,352	11.089	0.067362
14	NEUROSCIENCE LETTERS	31,037	2.105	0.057594
15	PAIN	29,045	5.777	0.047265
16	EUROPEAN JOURNAL OF NEUROSCIENCE	27,773	3.631	0.072392
17	NATURE REVIEWS NEUROSCIENCE	24,316	30.445	0.106125
18	PSYCHOPHARMACOLOGY	24,154	4.077	0.038764
19	EXPERIMENTAL BRAIN RESEARCH	20,138	2.395	0.035900
20	CEREBRAL CORTEX	19,105	6.544	0.072771
21	NEUROPSYCHOLOGIA	18,937	3.636	0.051540
22	NEUROPSYCHOPHARMACOLOGY	18,318	7.991	0.053454
23	TRENDS IN NEUROSCIENCES	17,821	14.235	0.045692
24	EXPERIMENTAL NEUROLOGY	17,739	4.699	0.038853
25	VISION RESEARCH	17,048	2.414	0.026900

Original publication of study 1

J Neurophysiol 111: 1238–1248, 2014.
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Electrical noise modulates perception of electrical pulses in humans: sensation enhancement via stochastic resonance

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Iliopoulos F, Nierhaus T, Villringer A. Electrical noise modulates perception of electrical pulses in humans: sensation enhancement via stochastic resonance. *J Neurophysiol* 111: 1238–1248, 2014. First published December 18, 2013; doi:10.1152/jn.00392.2013.—Although noise is usually considered to be harmful for signal detection and information transmission, stochastic resonance (SR) describes the counterintuitive phenomenon of noise enhancing the detection and transmission of weak input signals. In mammalian sensory systems, SR-related phenomena may arise both in the peripheral and the central nervous system. Here, we investigate behavioral SR effects of subliminal electrical noise stimulation on the perception of somatosensory stimuli in humans. We compare the likelihood to detect near-threshold pulses of different intensities applied on the left index finger during presence vs. absence of subliminal noise on the same or an adjacent finger. We show that (low-pass) noise can enhance signal detection when applied on the same finger. This enhancement is strong for near-threshold pulses below the 50% detection threshold and becomes stronger when near-threshold pulses are applied as brief trains. The effect reverses at pulse intensities above threshold, especially when noise is replaced by subliminal sinusoidal stimulation, arguing for a peripheral direct current addition. Unfiltered noise applied on longer pulses enhances detection of all pulse intensities. Noise applied to an adjacent finger has two opposing effects: an inhibiting effect (presumably due to lateral inhibition) and an enhancing effect (most likely due to SR in the central nervous system). In summary, we demonstrate that subliminal noise can significantly modulate detection performance of near-threshold stimuli. Our results indicate SR effects in the peripheral and central nervous system.

detection enhancement; perception modulation; somatosensoric threshold; subliminal electrical noise stimulation; unconscious noise

NOISE HAS A KEY ROLE IN SENSORY processes of biological systems (Collins et al. 1996a; Douglass et al. 1993; Ivey et al. 1998; Juusola and French 1997; Levin and Miller 1996). Usually, noise is considered to be detrimental for signal detection and information transmission since with increasing noise a marker of signal quality, the "signal-to-noise ratio," obviously decreases. Under certain conditions, however, noise can enhance the detection and transmission of weak input signals (Collins et al. 1996a,b; Douglass et al. 1993; Juusola and French 1997; Levin and Miller 1996). This paradoxical weak input enhancement is a manifestation of stochastic resonance (SR), a phenomenon that takes place in certain bistable nonlinear systems characterized by a delimiting barrier. In sensory systems, "the barrier" is the sensory detection threshold (ST), and according to SR theory there is a particular nonzero level of noise that forces undetectable stimuli to overcome the ST, thus improving the detection performance of the system.

A key question for the understanding of SR mechanisms in higher organisms is whether the interaction between noise and weak input signal occurs already and only in the peripheral nervous system or whether central processes, i.e., in the spinal cord and/or the brain, also play a role. Experiments that test for SR occurring in the central nervous system (CNS) are designed to deliver noise and input signal to different peripheral sensory pathways to ensure that the interacting signals converge only in the CNS.

Numerous studies have shown SR occurrence in animal sensory systems (Bahar et al. 2002; Collins et al. 1996a; Douglass et al. 1993; Freund et al. 2002; Ivey et al. 1998; Jaramillo and Wiesenfeld 1998; Juusola and French 1997; Levin and Miller 1996; Manjarrez et al. 2003). These organisms exhibit SR behavior by exploiting extrinsic noise to optimize performance on survival-related tasks, mostly feeding or predator avoidance. Since such complex behavior implicates higher cognition, memory and/or connectivity processes, researchers assumed SR phenomena to take place in the CNS. The first robust empirical findings that confirmed this notion were published by Manjarrez et al. in 2003. In a study on anesthetized cats, SR was demonstrated to occur in spinal and cortical evoked field potentials elicited by tactile stimuli providing the first proof for SR taking place in animal CNS (Manjarrez et al. 2003). Evidence for SR-related phenomena in humans has also been accumulated over the past 2 decades for the auditory (Morse and Evans 1996; Ward et al. 2001; Zeng et al. 2000), visual (Kitajo et al. 2003; Piana et al. 2000; Simonotto et al. 1999; Ward et al. 2001), and tactile sensory system (Collins et al. 1997; Priplata et al. 2002, 2003; Richardson et al. 1998). Several studies have been performed within one sensory modality with either noise and target signal being of the same or similar stimulation type (e.g., random vibration-weak mechanical indentations; Collins et al. 1996b) or of a different stimulation type (e.g., within the somatosensory system, the effect of electrical noise on the detection of mechanical indentations has been investigated; Richardson et al. 1998). Other studies have shown that SR interactions in humans can also occur between signals of different sensory modalities (cross-modal, e.g., auditory noise enhances visual, tactile, and proprioceptive sensory input; Lugo et al. 2008; Manjarrez et al. 2007).

The somatosensory system has been a main target to investigate improvements of performance with SR (e.g., Magalhães

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and Kohn 2011; Mendez-Balbuena et al. 2012). Based on SR, there is indeed some hope to come up with clinical applications. For example, Kurita et al. (2011) designed a wearable sensorimotor enhancer that improves tactile performance by implementing vibrotactile noise on the fingertips of humans. This peripheral vibrotactile enhancement (Collins et al. 1996b; Priplata et al. 2002; Richardson et al. 1998) is a well-proven effect that enhances the perception of tactile stimuli through SR. Despite these promising perspectives, however, so far some crucially important features for designing and optimizing SR effects in the somatosensory system are unclear, e.g., the optimal timing of "noise signals" in relation to the "test signal" is not known. Furthermore, the current understanding of the neurophysiological mechanisms that underlie SR is extremely limited, e.g., such basic issues as the neural sites of SR (peripheral vs. central?) and its relationship to other neurophysiological events (e.g., lateral inhibition) are poorly studied. We believe that this information is needed to implement "noise enhancement" effectively in both healthy and pathological conditions. The current study aims to give answers to some of these basic questions. To do so, we investigated the interaction of well-defined electrical pulses with simultaneously applied electrical noise (electrical noise stimulation, ENS). This setup can be "controlled" very flexibly and enabled us to build "our model" step by step all the way to the CNS focusing on the temporal interaction between the two signals without eliciting cross-modal effects.

In the first experiment, we investigated the most "trivial" case: noise and single electrical pulses applied on the same sensory input, which, via electrodes attached to individual fingers, was the peripheral finger nerve. By directly stimulating the same peripheral nerve, potential effects arising from receptor transductions such as temporal delays or nonlinear transductions are avoided. To get a detailed view of the synchronous interaction between the two signals, in the next experiment, instead of uniform pseudo-Gaussian distribution, ENS intensity was replaced by a sinusoidal function. After having shown selective enhancement in our model, we investigated the interaction between noise and pulses in somewhat more detail. To test whether the SR effect is purely peripheral, ENS was delivered not only on the same, but also on the adjacent finger. Also, in one experiment, single pulses were replaced by trains of pulses. Whereas in the aforementioned experiments, low-pass noise ("slow ENS") and short test pulses (0.2 ms) were used, in another experiment the noise signal was unfiltered ("fast ENS") and combined with long (10-ms) test pulses to allow for noise fluctuation during the application of the test pulses. In this last experiment, a forced-choice paradigm was used to assess sensitivity as a function of signal power.

Thus, in a series of experiments, we systematically varied stimulation and noise characteristics to get closer to the underlying mechanisms. Specifically, we addressed the following questions: *1*) under which conditions does subliminal noise lead to facilitatory and/or inhibitory effects on the detection of somatosensory stimuli applied to the same or the adjacent finger; and *2*) are there any signs for SR occurrence, and if so is this a result of signal interaction in the peripheral nervous system and/or CNS?

MATERIALS AND METHODS

All experiments were performed at the Department of Neurology at Charité Hospital (Charité - Universitätsmedizin Berlin, Campus Mitte). The protocols were approved by the local ethics committee; participants gave informed, written approval before participation and had no history of neurological or psychiatric disorder.

Electrical finger nerve stimulation was performed with a bipolar constant-current stimulator (DS5; Digitimer, Welwyn Garden City, Hertfordshire, United Kingdom) and steel wire ring electrodes. All signal waveforms were created using LabVIEW and generated as analog voltage signals through a National Instruments (NI) 6229 data acquisition (DAQ) card (Fig. 1). The analog outputs were channeled in two DS5 stimulators, which convert the voltage signal in current (direct current, DC) by constantly measuring the conductivity of the subject's finger. All current signals were concurrently measured and recorded in the analog inputs of the DAQ card. Further analysis was based on these recordings. The DS5 apart from stimulating also acted as an isolator to ensure the subjects' safety.

Electrodes were fixated using small pieces of polymeric sponge in a stable and comfortable position, making sure that the lateral sides of the finger were well in contact with the electrode. Typical distances between the electrodes were ~1.5 cm depending somewhat on the anatomic features of the subjects' fingers. After electrode fixation, a gel that facilitates conductivity was applied on the metal-cutis contact. The gel contained natriumchloride, hydroxyethylcellulose, propyl englykol, and sterilized water. In *experiments 1* and *2*, three electrodes were placed on the left index finger (all subjects were right-handed). For *experiments 3–5*, two additional electrodes were placed on the adjacent middle finger (Fig. 1). Stimulation of an adjacent finger excludes signal interaction in the peripheral nervous system; hence, any interaction is assumed to take place in the CNS.

Target pulses were single monophasic square-wave pulses with a duration of 200 μs generated at 5-kHz sampling rate, which is the maximum sampling frequency of the implemented acquisition card. Trials were presented at jittered interstimulus intervals (ISI) between 2.0 and 3.3 s. ISI randomization followed a uniform distribution. The noise signal had a zero-mean Gaussian distribution and was low-passed at 200 Hz. Noise was delivered in blocks of 20-s duration, always in an intermitted sequence (20-s noise on, 20-s noise off, and so on; Fig. 2). Both signals were recorded along with the subjects' responses using the same sampling frequency.

Before starting to record measurements, participants received training during which they were presented test pulses of various intensities and were made comfortable in identifying them. At the beginning of

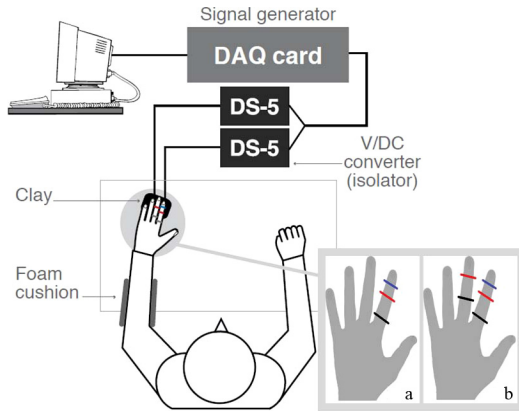


Fig. 1. Experimental setup. a: Electrode placement when both noise and pulses are applied on the same (index) finger. b: Electrode placement for noise stimulation on the same (index) or adjacent (middle) finger. Black, common ground; red, noise signal electrode; blue, target pulse electrode. DAQ, data acquisition; DS-5, Digitimer DS5 bipolar constant-current stimulator; V/DC, voltage/direct current.

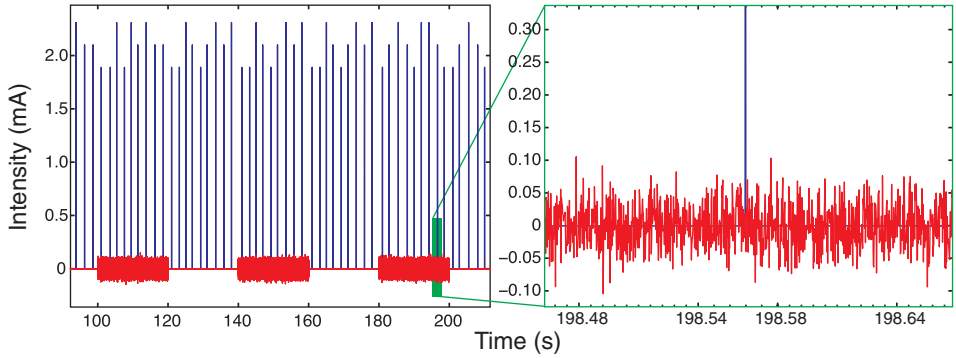


Fig. 2. *Left*: subliminal noise signal is applied in blocks of 20-s duration in an alternating pattern. *Right*: trace of a single pulse delivered during a continuous noise block.

all measurements, the ST of each participant was determined following the method of limits and subsequent forced choice (Windhorst and Johansson 1999). The detection rate values used to calculate the ST and in the subsequent analysis are given by:

$$\text{number of detected trials/total number of presented trials.} \quad (1)$$

The peak-to-peak noise level value used in all subsequent measurements was calculated based on this ST value. The noise level was maintained subliminal throughout all measurements in this study (equaled 0.05 × ST as long as the detection curve was valid and well-centered on the 50% of detected trials). We checked for subliminality of each noise level by asking the subjects to press a button immediately if they felt any kind of stimulation during a 20-s noise block. After each 20-s block, we asked the subjects once more whether they had felt anything.

In those experiments in which two fingers were involved, electrodes were placed on both fingers. Subjects were not told which finger was stimulated, and they were asked whether they perceived any stimulus in general without specifying the stimulated finger. We made sure that this noise level remained subliminal throughout the whole measurement by consulting the subject after every measurement. If the subject detected any kind of stimulation in any finger during this step or any stimulation on *finger 3* (which never received test pulse stimulation), this participant would have been excluded. This, however, never actually happened.

Before and after each run, the detection threshold was determined again, and the intensity of the near-threshold pulses in the respective subsequent run was adjusted accordingly.

Single pulses vs. single pulses with noise at the same finger. Subjects were asked to respond as fast as possible after any felt test pulse by pressing a button using their right thumb. Single monophasic square-wave pulses of three different intensities were applied, 10% below ST, 10% above ST, and on the ST calculated value, and noise was delivered in blocks of 20 s. Four runs were performed per subject on a total of 10 healthy subjects (4 men, 6 women, age 20–34 yr). Each measurement had a duration of 5.33 min, and a total of 144 trials was presented.

Single pulses vs. single pulses with sinusoidal noise at the same finger. In this experiment, the exact same protocol as in *experiment 1* was followed. The only alteration was that the subliminal noise signal was replaced by a 30-Hz subliminal sine signal (Fig. 3). Four 5.33-min measurements were performed per subject on a total of 10 new healthy subjects (6 women, 4 men, age: 19–36 yr).

Single pulses vs. single pulses with noise at the same or adjacent finger. In this configuration, pulses were continuously delivered to the index finger while noise was applied either to the index finger or alternatively to the adjacent finger. Following the same paradigm as before, noise was delivered in blocks of 20 s. Noise blocks were applied in a pseudorandomized sequence. Four measurements of 5.33-min duration were repeated per subject on a total of 11 healthy subjects (6 women, 5 men, age: 22–33 yr).

Pulse trains vs. pulse trains with noise at the same or adjacent finger. For a better understanding of the simultaneous single stimulus-noise interaction, this experiment was performed by presenting pulse trains instead of single pulses. In each trial, a train of 6 pulses was presented (10 Hz; Fig. 4). Again, subjects were instructed to respond as fast as possible every time they felt a test stimulus. The protocol, the block pseudorandomization, the noise features, as well as all of the remainder of the parameters in this configuration were identical to those in *experiment 3*. We measured 11 healthy subjects (6 women, 5 men, age: 22–34 yr).

Long single pulses vs. long single pulses with fast noise at the same or adjacent finger. In contrast to all previous configurations in which noise and target signal interacted simultaneously for 200 μs, maintaining a single intensity value for this interval, in this experimental arrangement, noise was not filtered, and each single pulse had 10-ms duration. This allowed the noise signal to shift polarity several times during each pulse (Fig. 5).

Furthermore, in this experiment, we followed an approach based on signal detection theory (SDT). In SDT, the sensitivity or discrimination capacity to a "real stimulus" is compared with a "null trial" typically in a forced-choice task, i.e., subjects are instructed to answer always with yes or no whether during a certain time period a pulse was felt or not. This leads to four different possible outcomes: a hit (correctly identified stimulus; H), a miss (negative response to an existing stimulus), a correct rejection, and a false alarm (identification of a stimulus when in fact it is absent; F). The most used index of SDT for calculating sensitivity is the sensitivity or discriminability index or just D′. D′ (Macmillan and Creelman 2005) is calculated from H and F through the inverse of the normal distribution function (z) also known as z-transformation:

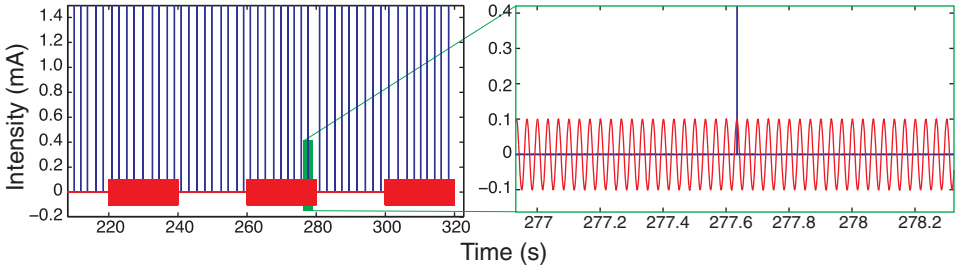


Fig. 3. *Left*: subliminal sine signal is applied in blocks of 20-s duration in an intermitted pattern. *Right*: trace of a representative full trial (a single pulse delivered on continuous subliminal sinusoidal stimulation).

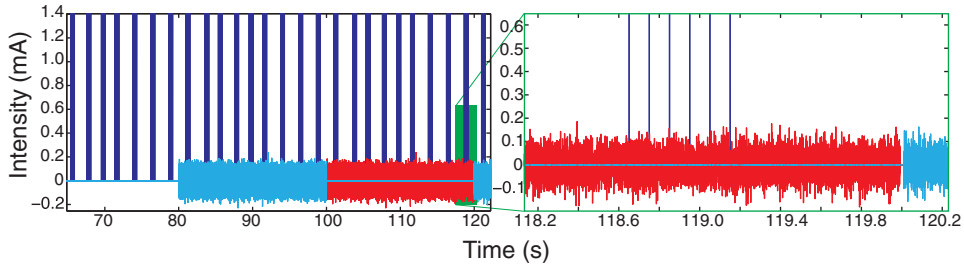


Fig. 4. *Left*: 2 subsequent blocks of noise: the 1st block is applied on the adjacent finger (light blue) and the 2nd on the index (red). *Right*: trace of a representative trial. A pulse train of 0.5-s duration (6 pulses at 10 Hz) was delivered during continuous noise stimulation.

$$D' = z(H) - z(F). \quad (2)$$

The temporal order of null trials and target trials was pseudorandomized. Each trial had a duration of 3.5 s. A single beep sound marked the beginning of each trial followed by a double beep sound 1.5 s after the first, indicating the moment of response. Between the acoustic markers, stimuli were presented with a 1-s time jitter. Noise was applied in 28-s blocks. Each condition ("just pulse," "pulse and noise on the index finger," "pulse on the index and noise on the adjacent finger," and "null trials") was presented in equal trial numbers for each subject.

RESULTS

Experiment 1: single pulses vs. single pulses with noise at the same finger. Figure 6 shows the detection rates for the averaged trials of all measurements for all subjects. The enhancement is higher when the test pulse intensity is lower. ENS induced a similar effect on 8 out of 10 subjects: a significant enhancement on the detection of the 2 lowest pulses and an insignificant decrease on the detection of the highest intensity pulses (Fig. 6). One out of 10 subjects improved performance for all 3 intensities, and 1 got worse in detecting all 3 intensities.

Experiment 2: single pulses vs. single pulses with sinusoidal noise at the same finger. In Fig. 7, the characteristic "twisting" effect of the 30-Hz sinusoidal function is seen. Trace analysis shows that the effect of the sine DC waveform on the coinciding pulses depends on the distribution of negative-positive values and the intensity of each pulse. A sine function has an equal distribution of negative and positive traces during each measurement. By using a sine signal, the sign trace distribution is maintained symmetrical throughout each measurement. Consequently, the "seesaw twist" effect on the grand average (Fig. 7) is more symmetrical than the noise effect (Fig. 6) as seen in the extreme pulse detection rates.

Both ENS/sine waveform and pulse signals in *experiments 1* and *2* described above were generated in the same sample frequency (5 kHz) as the single pulses. Hence, whenever a pulse was delivered simultaneously with noise, the two signals interacted "instantly" for 200 μs (sum trace interval). The value of the applied intensity of the sine waveform in the same moment a pulse is delivered is a sine intensity trace. A trace analysis was performed in all such traces to identify common attributes of successfully detected vs. undetected traces (Fig. 8).

The analysis of the instantaneous noise (or sinusoidal) intensity during the 200-μs time period of near-threshold pulse application showed that simultaneous voltage addition in the nerve seems to play a key role for the detection enhancement mechanism between target and sine signal. Figure 8, *right*, illustrates that when stimulating using a sinusoidal signal the sum of the simultaneous DC addition between sine trace and test pulse intensity is what determines whether a test pulse is detected. Positive sinusoidal traces improved the detection of the test pulses, which by default are always positive. From the *top* row (Fig. 8, *right*), it can be derived that negative sine traces increased the likelihood of pulses to remain undetected. In the case of the lowest intensity, most of the trials are undetected when ENS is absent. Negative DC values have no real effect on pulses of this intensity since already undetected trials remain undetected. The opposite effect takes place for the highest intensity, i.e., negative noise values decrease the detectability of the highest intensity pulses. Whether pulses of the middle intensity are becoming more or less detectable depends on the sign distribution that coincides with pulses of this intensity. A positive DC "population" increases detection rates, whereas negative DC values tend to reduce detection rates for pulses of this intensity (Fig. 8, *right*).

Experiment 3: single pulses vs. single pulses with noise at the same or adjacent finger. ENS when applied on the adjacent finger had no significant effect on the detection of pulses at the two lowest intensities. The only significant effect of ENS on the adjacent finger was the decrease of the detection rate of the highest intensity pulses ($P = 0.00486$ and 0.0266 for ENS at the same and adjacent finger, respectively; Fig. 9).

Experiment 4: pulse trains vs. pulse trains with noise at the same or adjacent finger. In this experiment, the highest detection rates occur when noise and pulse trains are both delivered on the index finger (Fig. 10). By using trains instead of single

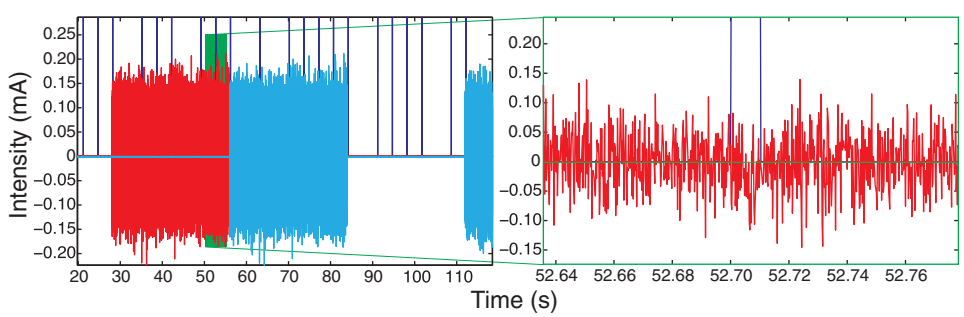


Fig. 5. Noise signal is applied in blocks of 28-s duration. *Left*: 2 subsequent blocks of noise: the block in light blue is applied on the adjacent (middle) finger, and the red noise block on the index finger. *Right*: trace of a representative full trial (a long pulse of 10-ms duration delivered on continuous fast noise stimulation).

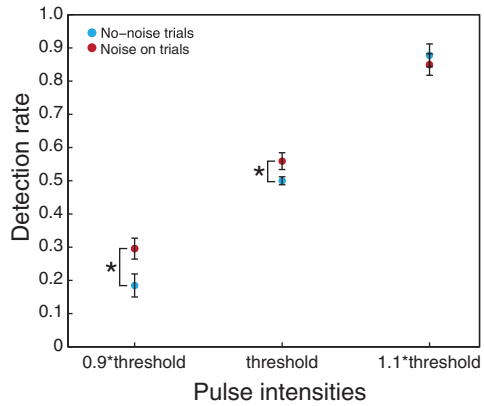


Fig. 6. *Experiment 1*. Grand average of all 10 subjects: red points correspond to trials detected during noise stimulation. Blue points represent trials detected without the presence of noise. *Significant effects on the lowest ($P = 0.00986$) and mid- ($P = 0.0389$) pulse intensities.

pulses, the probability of a positive noise trace to coincide with a part of the target stimulus increases. The more single pulses are contained in a pulse train, the higher this probability. The detection rate for the highest intensity pulses (always close to 100%) remains unaffected. Subliminal ENS applied on the same finger significantly increases the total detection rates of all near-threshold pulse trains, thus shifting the ST of the subjects toward lower values. This total detection rate enhancement occurred for all 11 subjects. Notwithstanding, subliminal noise applied on the adjacent finger induced a significant decrease ($P = 0.0389$) of the highest intensity detection rate that reaffirms the effect also seen using single-pulse stimuli (*experiment 3*).

Experiment 5: long single pulses vs. long single pulses with fast noise at the same or adjacent finger. The D′ analysis results demonstrates that the subjects became significantly more sensitive in detecting pulses of the two lowest intensities when noise was applied on the same finger (Fig. 11). Moreover, noise applied on the adjacent finger also improved the likelihood for detection of near-threshold pulses, particularly for pulses of midintensity. Although this partial enhancement was not statistically significant ($P = 0.0600$), the total detection rates for trials of all 3 pulse intensities are significantly higher during the presence of adjacent ENS ($P = 0.0364$). More important, 7 out of 12 subjects exhibited both a significant improvement on the detection rates and on the D′ values for the 2 lower intensities. We corrected for undefined ($\pm\infty$) values of hit and false alarm rate by adding 0.5 to all data cells (hits, misses, false alarms, and correct rejections) before calculation (Hautus 1995; Miller 1996). Six subjects scored zero false alarms, five subjects scored one single false alarm, respectively (the wrongly identified test pulses actually occurred in different trials), and one subject scored two false alarms. Two of the false alarms corresponded to null trials in complete signal absence, three were committed during subliminal ENS on the adjacent finger, and two false alarms were given during ENS at the same finger (both responses given by the same subject).

The slightly higher rate of false alarm responses in *experiment 5* compared with *experiments 1–4* (along with an overall different performance as seen in the D′ plots) may be due to the somewhat increased overall attention associated with trials in *experiment 5* based on the forced-choice setup; furthermore, there were differences in the applied signals (faster noise and longer pulses), and there was also a different time jitter.

However, given that there was never any significant number of false-positive hits and also never any significant change of false-positive hits by additional noise, we can conclude that the enhancing effect (of D′) of additional noise is mainly driven by the increase of the hit rate to actual stimuli.

As for *experiments 1–4*, they did not follow a strict "forced-choice design": rather, before each experimental block, subjects were asked to report immediately whenever they felt any stimulation. In these experiments, we never had any false alarm, and (formally) no responses to "pseudonull[1] trials" (which we inserted retrospectively) were given, i.e., all responses followed test pulses.

Figure 12 gives the result of a binning analysis performed by calculating the noise signal power applied along (during) each pulse stimulus. First, we segmented the parts of the noise waveform contained in each test pulse stimulation (Fig. 5). Then, we calculated the noise power deposited to the finger during each test pulse using the mean square root of each noise segment:

$$\text{power of noise segment} = \sqrt{(\text{noise segment})^2}. \qquad (3)$$

After sorting the trials according to the respective noise power, trials were classified in five equidistant zones (bins). Each group containing trials of the same power noise (as calculated in *Eq. 3*) is defined as a noise power bin. Trials belonging to the same noise power bin are trials during which the same amount of electrical energy was deposited on the nerve. Since the pulse presentation was uniformly randomized, each bin would be as likely to contain the same number of trials. In this sense, the "bin distribution" is uniform as well. For each bin, a D′ value is determined after taking the corresponding "null trials responses" into account. This process was followed separately for each of the three pulse intensities.

Regarding the detection enhancement of the lowest-intensity pulses, 7 of the 12 subjects exhibited classic SR-type behavior: as the intensity of the input electrical noise increased, D′ increased likewise to a peak and then decreased back to the same initial values (Fig. 12). In 2 of the other subjects, D′

[1] "Pseudo" since there was no cue to announce a trial or a decision.

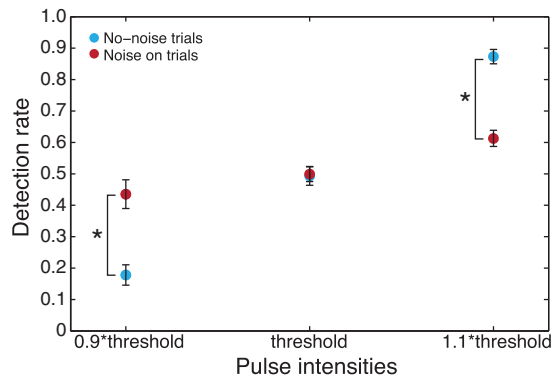


Fig. 7. *Experiment 2*. Grand average of all 10 subjects: red points correspond to trials that were detected during subliminal sinusoidal stimulation. Blue points represent trials detected without the sine-noise signal. *Significant effect on the extreme intensities ($P = 0.000924$ on the lowest intensity, $P = 0.001038$ on the highest).

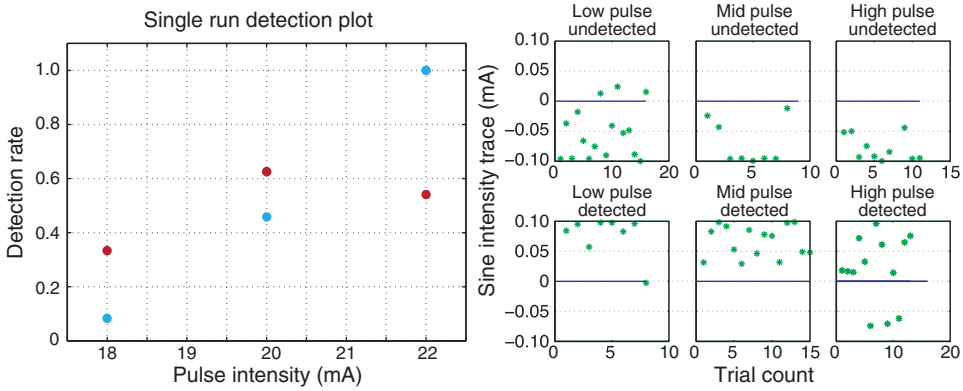


Fig. 8. Trace analysis for a representative single run of *experiment 2*. *Left*: detection plot for a single run (24 trials per point). *Right*: sine intensity trace is the momentaneous intensity value of the sinusoidal noise waveform on the instant a test pulse was delivered so that points correspond to the value of the sinusoidal noise signal the moment a single pulse was delivered along with the noise. DC addition effect: the addition of negative sine intensities causes more trials to be undetected (*top* row), whereas the addition of positive sine traces leads to significantly more detectable trials (*bottom* row).

reached a significant peak for the maximum noise level. In this case, the noise intensity range may be limited to the 1st half (increasing portion) of the classic SR curve. Regardless, in 9 of 12 subjects, the introduction of a particular level of electrical noise on the index finger significantly enhanced their overall ability to detect near-threshold electrical stimuli.

DISCUSSION

We tested SR effects for electrical stimulation of finger nerves. Specifically, we show that the addition of subliminal noise enhances detection performance, particularly of pulse intensities below the 50% threshold, whereas detection of pulses above ST tends to be worsened. A similar effect is seen for subliminal sinusoidal stimulation. The effect becomes stronger when, instead of single near-threshold pulses, pulse trains are applied. Noise applied on an adjacent finger has two opposing effects. Low-pass filtered noise worsens detection of pulses above ST, and this applies for both single pulses as well as pulse trains. Unfiltered (fast) noise, however, on the adjacent finger is shown to enhance detection. To the best of our knowledge, this is the first time that these fundamental and basic questions concerning the effect of ENS on the detection of near-threshold pulses are answered.

Previously, it has been shown that the addition of noise can lead to improvements for various processes in humans. Enhancing effects have been reported for different noise modalities: the addition of mechanical noise has been shown to improve postural control and balance (Priplata et al. 2002, 2006; Reeves et al. 2009) and blood pressure regulation (Hidaka et al. 2000) and enhance the detectability of weak tactile stimuli (Collins et al. 1996b, 1997; Ivey et al. 1998). Acoustic noise has been shown to improve tone perception (Lugo et al. 2008; Tanaka et al. 2009; Ward et al. 2010) as well as tactile, visual, and proprioceptive sensations (Lugo et al. 2008), whereas optical noise was shown to increase performance in visual as well as in sensorimotor tasks (Kitajo et al. 2003).

In contrast to these noise modalities that act primarily on receptors in the respective sensory system, ENS directly stimulates the nerve fiber that permits assessing precise timing characteristics of the interacting signals. The circumscribed local effect and the precise timing allow for tracking specific pathways in the peripheral system as well as in the CNS, a unique property of the electrical modality. Various studies performed using electrical noise showed enhancing effects emerging by implementing ENS peripherally or in the CNS. Electrical noise has been shown to improve postural control and balance (Gravelle et al. 2002; Mulavara et al. 2011; Reeves et al. 2009) and detectability of weak tactile stimuli (Richardson et al. 1998) and enhance spindle function (Cordo et al. 1996). Additionally, Yamamoto et al. (2005) showed that galvanic vestibular noise stimulation improves autonomic and motor responsiveness, and Terney et al. (2008) showed that transcranial random noise stimulation has an important, enhancing, general impact on brain excitability as seen through cognitive, learning, and motor tasks. This creates expectations for central ENS to evolve into a technique that may facilitate

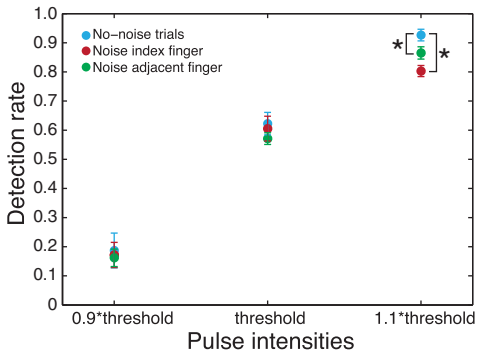


Fig. 9. *Experiment 3*. Grand average of all 11 subjects: blue points correspond to trials detected on absence of noise. Red points correspond to trials detected during noise stimulation on the index finger. Green points correspond to trials detected during noise stimulation on the adjacent finger. *Significant effects on the highest intensity.

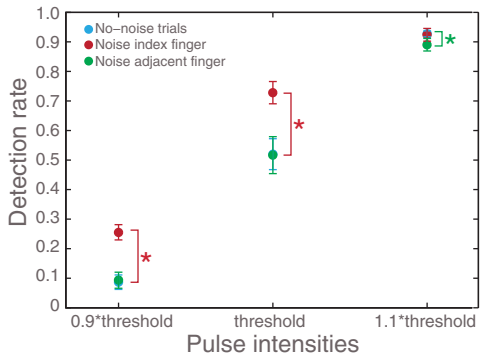


Fig. 10. *Experiment 4*. Grand average of all 11 subjects: blue points are pulse train trials detected on absence of noise. Red points correspond to trials that were detected during noise stimulation on the index finger. Green points correspond to trials that were detected during stimulation on the adjacent finger. When both noise and stimuli are applied to the same finger, the total detection rates are significantly higher on the presence of noise. *$P = 0.00105$ and 0.000814 for noise at the lowest and middle intensity, respectively.

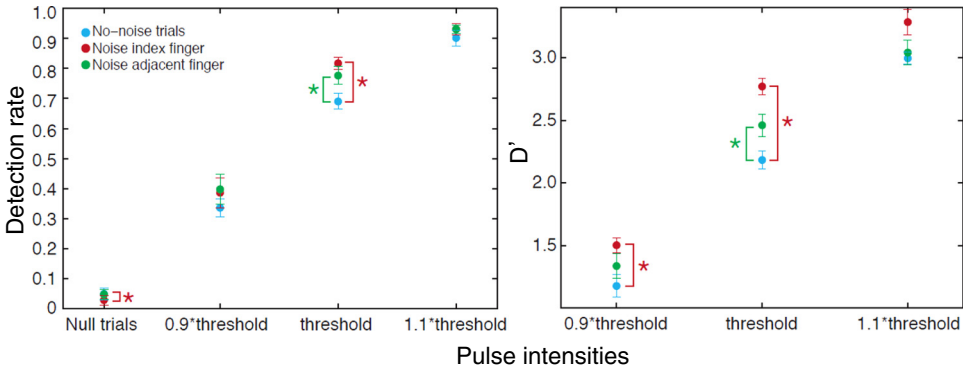


Fig. 11. *Experiment 5*. Grand average of all 12 subjects: blue points correspond to long pulses applied without the presence of noise. Red points correspond to long pulses applied during unfiltered noise stimulation on the same finger. Green points correspond to long pulses applied during noise stimulation on the adjacent finger. *Left*: proportion of "Yes" rates of detected trials. *Right*: discriminability index (D′) plots. *Significant increase in total detection rates when both noise and stimuli are applied to the same and to the adjacent finger.

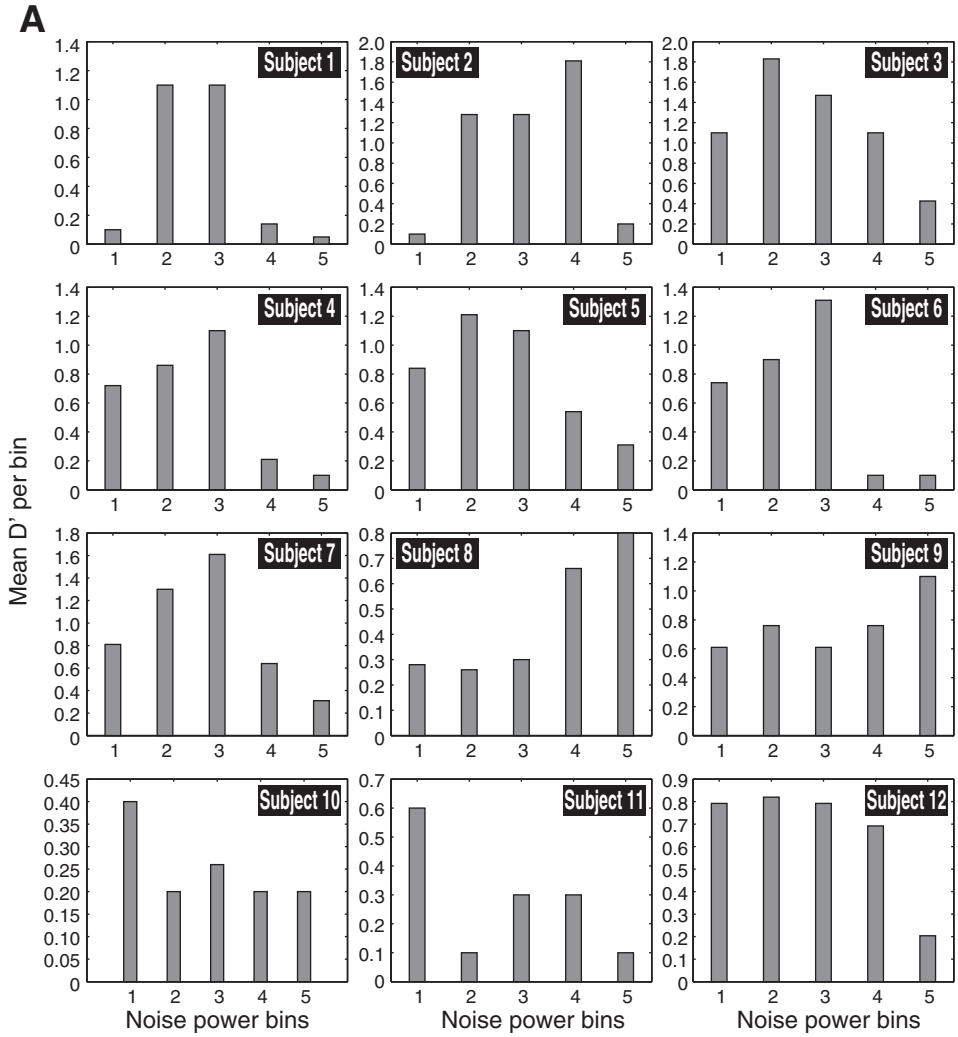
different types of synaptic transmission in the brain, potentially improving higher cognitive functions.

In our experiments, we carefully selected ENS amplitude such that it was always clearly subliminal. Pilot testing showed that slow (low-passed) ENS is more likely to be felt than fast (unfiltered) ENS. A typical magnitude difference in our test results is that a fast (5-kHz) ENS signal would start to become supraliminal for an amplitude range ~10 times higher than the corresponding slow (low-passed at 200 Hz) ENS signal for the same subject. Most probably, this is due to the fact that faster shifts of polarity leave less time for ions to transit the semipermeable membrane, making action potentials less likely to occur. This finding differentiates the effect of electrical noise on the somatosensory system from other types of noise modalities: e.g., for vibrotactile noise, it has been shown that the slower the signal, the less likely receptors were excited (Collins et al. 1997). In this case, the excitation of rapidly adapting afferents is limited when the mechanical noise is low-passed at 30 Hz.

In all studies, we tested how the addition of a subliminal "background" noise influenced the detection of near-threshold stimuli pursuing the hypothesis (McDonnell and Abbott 2009): detection (subliminal noise + near-threshold stimuli) > detection (near-threshold stimuli). We show that enhancement depends on the relative attributes of the target (pulses) and the noise signal. In *experiment 5*, we have followed a SDT approach, ENS is faster, and the test pulses are longer than before. Consequently, one cannot make quantitative direct comparisons between the effects of fast and slow ENS (implemented in *experiments 1–4*) based on the data of the present study. Still, the dynamic temporal relationship between the interacting signals affirms a crucial general remark: when noise is relatively slow as to the target signal, i.e., frequency content (ENS) ≤ frequency content (pulses), and both signals are applied to the same peripheral nerve (index finger), enhancement occurs only for the lowest test pulse intensity. In the same experiments, higher-intensity pulses, however, become harder to detect while noise is present. Hence, in this paradigm (*experiments 1* and *2*), there is a tradeoff between selective enhancement and selective inhibition. Interestingly, the overall ability of the subjects to perceive near-threshold pulses as indexed by the total detection rate of all pulses remains approximately constant with and without ENS (*experiment 1*). Thus the effect of slow noise could be utilized to enhance or reduce detection of the extreme pulses, respectively, but there is another interesting implication of this seesaw twist effect. Considering that the slope of a sigmoid detection curve is an analog of the transfer gain function (system theory), noise in this context can serve as a transfer function moderator (Freeman 1975, 1991; Gordon 1990; Skarda and Freeman 1987). Since a fundamental behavioral attribute classically associated to the slope of such curves is arousal, slow noise could play the role of an arousal moderator/modulator in similar electrical stimulation tasks.

The analysis of instantaneous signal interaction (Fig. 8) demonstrates that the instantaneous addition of noise (or sinusoidal noise) and the pulse amplitude plays a major role for signal detection as postulated by SR. This "DC addition mechanism" becomes most evident when noise is replaced by subliminal sinusoidal stimulation (*experiment 2*). Here, the equibalanced distribution between positive and negative DC additions elicited a strikingly symmetrical seesaw twist (Fig. 7). Comparing the effect of sinusoidal stimulation with the effect of noise, it seems that the effect of noise cannot be fully explained by DC addition/subtraction since the noise effect seems to lack a clear symmetry (regarding the enhanced perception of low-intensity pulses vs. the attenuated perception of high-intensity pulses) as seen when comparing Figs. 6 and 7. Clearly, this issue requires further investigation.

In *experiment 5*, where unfiltered (fast) noise interacts with longer pulses, pilot testing showed that subjects were incapable to distinguish between the longer (10-ms) and the shorter (200-μs) pulses even after adjustment for intensity, i.e., typically a subject with a 2.1-mA threshold for short and 0.72-mA for long pulses would sense these two pulses identically. By submitting the participants to a forced-choice task, we followed a SDT approach. Detection in the hypothesis for this experiment now stands for the subjects' sensitivity in perceiving all near-threshold single pulses. In this paradigm, ENS targeted to the index finger led to a powerful enhancement of sensitivity as D′ gets larger. By analyzing the impact of the summed input (by binning the sums of test pulse intensity and instantaneous noise), we show that the effect of noise addition for the lowest-intensity pulses follows the classic inverse U-shape SR curve (Fig. 12). This is strong evidence that SR effects dominate detection at this pulse intensity since detection enhancement is driven by noise power. Binning analysis on the two other intensity pulses did not show a consistent behavioral pattern. Since the possible enhancement depends on the intensity of the pulse itself, it is possible that the range of noise amplitudes implemented was not wide enough; i.e., the tested region may have been limited to a partial portion (ascending half) of the SR curve for the specific intensity.



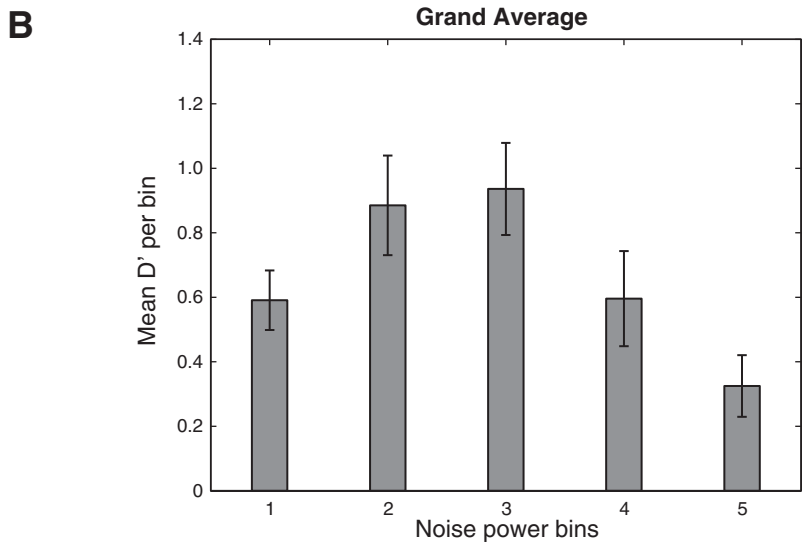


Fig. 12. *A*: values of D′ for lowest-intensity pulses vs. the normalized noise power bins (5 bins of equidistant amplitude zones, noise applied to the index finger) for all 12 subjects. *Subjects 1–7* as well as *subject 12* exhibited clear stochastic resonance (SR) behavior: as the intensity of the input electrical noise increased, D′ increased to a significant peak and then decreased again. In *subjects 8* and *9*, detection was maximal for the highest noise level. Perhaps, in this case, the applied noise amplitude ranges included only the "ascending half" of the SR curve, i.e., the range of noise amplitudes was not wide enough to cover fully the SR effect. *Subjects 10* and *11* showed no clear effect. *B*: the grand average of all 12 subjects reveals the classic SR inverse U-shape curve.

At this point, a theoretical clarification needs to be made: a well-known method that also exploits noise in signal detection is dithering, which is an antialiasing technique that uses noise in quantization (or requantization) processes as to randomize quantization error. When added to low-amplitude or highly periodical signals before any digital sampling, dithering decorrelates the quantization error from the input signal, and any remaining distortion will exhibit a random distribution after sampling, i.e., a kind of "noise smoothing" is achieved. In this context, the seesaw effect that we found in *experiments 1* and

2 may be described as dithering. The term SR is usually used when aiming at a general detection enhancement of near-threshold signals that is driven by (an optimal) noise power (McDonnell and Abbott 2009; Wannamaker et al. 2000) as shown by an inverse U-shape relationship between noise power and signal detection. Hence, the results of *experiment 5*, in which at certain powers of (fast!) noise the detection of near-threshold pulses is generally enhanced, most clearly meet that terminology. Nevertheless, the underlying mechanisms may be similar if not the same for dithering and SR, namely, signal addition at quantization or detection thresholds, respectively. Therefore, one may generally speak of "noise-induced threshold crossings" (Gammaitoni 1995). The aim of SR in its more narrow definition may best be achieved if noise has the features used in *experiment 5* (fast compared with the target signal). Thus the SR approach followed in this study (hypothesis; McDonnell and Abbott 2009) acknowledges that the terms SR and dithering are not mutually exclusive, but rather refer to different situations of using noise to influence signal detection.

When (low-pass) noise signal was applied to the adjacent finger (*experiments 3* and *4*), subjects became significantly worse in detecting single pulses of the highest intensity. The detection rates of the two less-intense near-threshold pulses (at threshold, 10% below threshold) remained unaffected (*experiment 3*). In principle, the same pattern was seen in *experiment 4*, in which pulse trains were used instead of single pulses. This pattern seems not consistent with SR; rather, lateral inhibition may play an important role here (Hsieh et al. 1995; Taskin et al. 2008). Lateral inhibition is a well-known phenomenon in sensory systems. There is an extensive overlap of adjacent finger representations in primary somatosensory cortex (SI), and ample evidence in literature suggests that principal neurons in humans and other primates have receptive fields that spread out to more than one finger, causing substantial overlapping finger representations (Iwamura et al. 1993; Schroeder et al. 1995; Smits et al. 1991). The overlap is more extensive for neurons located in the caudal subarea of SI. The overlap is particularly noticeable when it comes to the representation of the human middle and the human index finger (Krause et al. 2001). A functional feature caused by this overlap is the sharpening of stimulus representation in space by inhibiting input from "neighboring" body parts (lateral inhibition). The presence of such lateral inhibition effects has been shown in both animal as well as human studies (Greek et al. 2003; Hsieh et al. 1995).

Whereas in these experiments no clear indication of SR effects of noise to an adjacent finger was found, *experiment 5* gives new evidence for a facilitatory effect of applying noise to the adjacent finger: the total detection rates became distinctly higher, i.e., there was a significant enhancement of the general ability of subjects to detect near-threshold trials. This finding strongly suggests a central component of SR in the CNS. Overall, the influence of ENS on an adjacent finger seems to be mediated by at least two opposing effects, i.e., lateral inhibition and SR. It seems that these effects differ with respect to their dependence on the strength of the target pulse and/or the precise temporal relationship between target pulses and noise. For example, the SR effect occurred mainly on the two lower intensities, whereas the inhibitory effect was seen at the highest intensity.

When the target stimuli are pulse trains instead of single pulses, the enhancement effect of ENS seems to be drastically stronger. Each single pulse corresponded to the shortest segment of signal that the implemented equipment could possibly generate (200 μs). Two positive segments employed simultaneously create a stronger stimulus that is more likely to be detected than each single stimulus applied separately. Therefore, the enhancement effect of subliminal noise is drastically stronger when using pulse trains for which the probability of two signal segments of positive voltage value coinciding in time is proportional to the extent of stochastic capability of the resonating system (Papoulis and Pillai 2001; Wio et al. 2012). Notably, there may also be an influence of periodicity within the pulse train stimulus. Periodically stimulated sensory neurons typically exhibit a statistical phase-locking to the stimulus (Dolnik et al. 1992; Longtin 1992). Periodic stimuli favor firing of neurons at a preferred phase of the stimulus cycle with peaks centered at integer multiples of the driving periods. The phase-locked effect has been shown to take place specifically for neurons involved in transducing electrical fields (Longtin 2002). Periodicity of the stimuli also has an impact on signal processing in the CNS since it can induce neural synchronization. Both intra- and interregional synchronization of neural activity induced by periodic input have been shown to be facilitated by the addition of moderate amounts of random noise (Ward et al. 2010). To disentangle the two effects (SR only vs. SR and effect of periodic stimulation), studies will have to be performed in which pulse trains are presented at irregular intervals.

In conclusion, this study shows that subliminal ENS stimulation can be used to improve perception of near-threshold electrical stimuli. Enhancement of detectability was achieved either for all near-threshold intensities (*experiments 4* and *5*) or selectively (*experiments 1–3*) by tuning the respective frequency content of the interacting signals. In the case of selective enhancement, there is a tradeoff between attenuation of pulses above threshold and facilitation of pulses under threshold; hence, ENS can serve as a transfer function modulator. Potential applications are numerous, including fine-tuning of brain-computer interfaces, control of surgical instruments, and implants such as cortical microarrays, real-time calibration of microcontrollers, pain modulation, informational feedback for monitoring and sensor devices, as well as haptic/sensory rehabilitation and sensorimotor adaptation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

F.I., T.N., and A.V. conception and design of research; F.I. performed experiments; F.I. and T.N. analyzed data; F.I., T.N., and A.V. interpreted results of experiments; F.I. prepared figures; F.I. and A.V. drafted manuscript; F.I., T.N., and A.V. edited and revised manuscript; F.I., T.N., and A.V. approved final version of manuscript.

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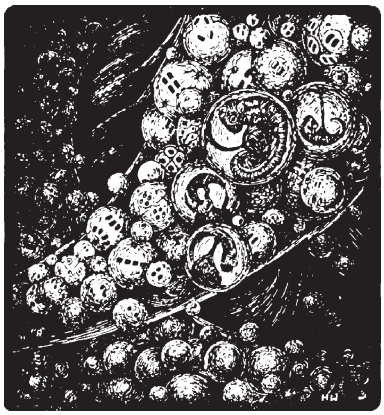

Publication 2

Iliopoulos F, Taskin B, Villringer A, Nierhaus T. Imperceptible somatosensory single pulse and pulse train stimulation oppositely modulate mu rhythm activity and perceptual performance. Cerebral Cortex. 2020. 30(12):6284-6295
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Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"NEUROSCIENCES"** Selected Category Scheme: WoS
Gesamtanzahl: 267 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	43,107	33.162	0.068480
2	NATURE NEUROSCIENCE	63,390	21.126	0.164700
3	ACTA NEUROPATHOLOGICA	20,206	18.174	0.041660
4	BEHAVIORAL AND BRAIN SCIENCES	9,377	17.194	0.010240
5	TRENDS IN COGNITIVE SCIENCES	27,095	16.173	0.040040
6	JOURNAL OF PINEAL RESEARCH	10,695	15.221	0.010560
7	NEURON	95,348	14.403	0.218680
8	TRENDS IN NEUROSCIENCES	20,163	12.314	0.024480
9	Annual Review of Neuroscience	14,042	12.043	0.015020
10	MOLECULAR PSYCHIATRY	20,353	11.973	0.049290
11	BRAIN	52,970	11.814	0.074030
12	BIOLOGICAL PSYCHIATRY	43,122	11.501	0.053320
13	PROGRESS IN NEUROBIOLOGY	12,929	10.658	0.013230
14	Nature Human Behaviour	1,230	10.575	0.006550
15	SLEEP MEDICINE REVIEWS	6,920	10.517	0.010920
16	ANNALS OF NEUROLOGY	37,336	9.496	0.048630
17	Molecular Neurodegeneration	4,248	8.274	0.011350
18	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	26,724	8.002	0.051580
19	FRONTIERS IN NEUROENDOCRINOLOGY	4,196	7.852	0.005490
20	Neurology-Neuroimmunology & Neuroinflammation	1,996	7.353	0.008220
21	NEUROPSYCHOPHARMACOLOGY	25,672	7.160	0.039090

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
22	Brain Stimulation	5,457	6.919	0.014470
23	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,876	6.878	0.006420
24	NEUROENDOCRINOLOGY	5,046	6.804	0.005690
25	NEUROSCIENTIST	4,986	6.791	0.008520
26	BRAIN BEHAVIOR AND IMMUNITY	14,533	6.170	0.025700
27	BRAIN PATHOLOGY	5,263	6.155	0.007880
28	Alzheimers Research & Therapy	3,160	6.142	0.010700
29	JOURNAL OF NEUROSCIENCE	175,046	6.074	0.233460
30	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,766	6.040	0.028050
31	PAIN	38,312	6.029	0.039070
32	CURRENT OPINION IN NEUROBIOLOGY	15,090	6.014	0.033650
33	Acta Neuropathologica Communications	3,063	5.883	0.014190
34	Translational Stroke Research	1,955	5.847	0.004330
35	GLIA	14,003	5.829	0.018760
36	NEUROIMAGE	99,720	5.812	0.132720
37	NEURAL NETWORKS	13,063	5.785	0.016060
38	NEUROPSYCHOLOGY REVIEW	2,971	5.739	0.003940
39	Molecular Autism	2,107	5.712	0.008000
40	Journal of Neuroinflammation	11,767	5.700	0.023240
41	Multiple Sclerosis Journal	11,501	5.649	0.022750
42	Annual Review of Vision Science	458	5.622	0.003300
43	Neurotherapeutics	4,475	5.552	0.009060
44	Translational Neurodegeneration	810	5.534	0.002420

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
45	CEREBRAL CORTEX	30,675	5.437	0.059570
46	JOURNAL OF PAIN	10,405	5.424	0.018280
47	NEUROBIOLOGY OF DISEASE	16,363	5.160	0.026710
48	NEUROINFORMATICS	1,277	5.127	0.002920
49	JOURNAL OF PHYSIOLOGY-LONDON	52,037	4.950	0.041100
50	BIPOLAR DISORDERS	5,143	4.936	0.006760
51	Developmental Cognitive Neuroscience	2,470	4.920	0.009240
52	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	3,293	4.899	0.004540
53	JOURNAL OF NEUROCHEMISTRY	35,902	4.870	0.026140
54	Dialogues in Clinical Neuroscience	3,384	4.867	0.004730
55	Annals of Clinical and Translational Neurology	1,858	4.656	0.008750
56	CURRENT OPINION IN NEUROLOGY	5,290	4.647	0.009650
57	MOLECULAR NEUROBIOLOGY	12,806	4.586	0.027560
58	SLEEP	21,434	4.571	0.024240
59	Current Neuropharmacology	3,508	4.568	0.005650
60	EXPERIMENTAL NEUROLOGY	20,500	4.562	0.023440
61	HUMAN BRAIN MAPPING	22,040	4.554	0.043230
62	Journal of Neural Engineering	7,336	4.551	0.012190
63	EUROPEAN NEUROPSYCHOPHARMACOLOGY	7,488	4.468	0.015500
64	CEPHALALGIA	9,983	4.438	0.014480
65	NEUROBIOLOGY OF AGING	22,409	4.398	0.037090
66	EUROPEAN JOURNAL OF NEUROLOGY	10,488	4.387	0.016970

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Original publication of study 2

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Original Article

ORIGINAL ARTICLE

Imperceptible Somatosensory Single Pulse and Pulse Train Stimulation Oppositely Modulate Mu Rhythm Activity and Perceptual Performance

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Abstract

Subliminal stimulation alters conscious perception – a potential mechanism is the modulation of cortical background rhythms especially in the alpha range. Here, in the human somatosensory domain, we assessed effects of subthreshold (imperceptible) electrical finger nerve stimulation – either presented as single pulses or as brief (1 s) 7 Hz pulse trains—on mu-alpha rhythm and perceptual performance. In electroencephalography, subthreshold single pulses transiently (~150–350 ms poststimulus) increased mu activity (event-related synchronization), while, interestingly, subthreshold trains led to prolonged (>1 s) mu desynchronization. In psychophysics, detection of near-threshold target stimuli was consistently reduced when presented together with subthreshold trains (at three delays), whereas for targets paired with subthreshold single pulses detection remained unaffected (30 and 180 ms) or was even elevated (60 ms). Though both imperceptible, single pulses and pulse trains exerted opposite effects on neural signaling and perception. We suggest that the common neural basis is preferential activation of cortical inhibitory interneurons. While the inhibitory impact of a subthreshold single pulse (reflected by mu synchronization) is not psychophysically detectable—rather perception may be facilitated—repetition of the same subthreshold pulse shifts the excitation-inhibition balance toward an inhibitory cortical state (reflected by perceptual impediment) accompanied by mu desynchronization. These differential findings provide novel insights on the notion of alpha activity mediating functional inhibition.

Key words: EEG alpha oscillations, event-related desynchronization/synchronization, inhibition, nonconscious, subliminal

Introduction

Weak sensory stimuli that escape conscious perception can still modulate brain function and context-dependent behavior. This has been repeatedly demonstrated in behavioral (Reingold and Merikle 1988; Dehaene et al. 2006; Bareither et al. 2014a; Baumgarten et al. 2017) as well as electrophysiological and neuroimaging studies (Kouider and Dehaene 2007; Del Cul et al. 2009; van Gaal et al. 2012; Bareither et al. 2014b). The various mechanisms, however, by which brain functions are modulated by imperceptible stimulation, remain poorly understood.

A potential mediator of the effects emerging from imperceptible stimulation is the modulation of neural oscillations: These are known to underlie fundamental brain functions such as motor control (Miller et al. 2007; Mazaheri et al. 2009; Sauseng et al. 2009), sleep (Massimini et al. 2004), memory (Klimesch 1999), and cognitive performance (Thut and Miniussi 2009;

Romei et al. 2010) as well as perception, where alpha power and phase play a crucial role (Busch et al. 2009; Mathewson et al. 2009; Cecere et al. 2015). Beyond the notion of an "idle" operational state (Pfurtscheller et al. 1996), cortical oscillations in the alpha band (~10 Hz) are commonly considered to represent functional inhibition observed on the behavioral level (Klimesch et al. 2007; Jensen and Mazaheri 2010). For instance, high posterior alpha power predicts reduced perceptibility of an upcoming weak visual stimulus (e.g., Ergenoglu et al. 2004; Babiloni et al. 2006; Hanslmayr et al. 2007; van Dijk et al. 2008) and, in attention-related tasks, regions that are not involved in stimulus-related processing exhibit stronger alpha power (Klimesch 2012). Furthermore, it has been shown that low prestimulus alpha power also translates into higher visually evoked blood oxygenation level-dependent (BOLD) signal (Becker et al. 2011) and that also the phase of alpha rhythm influences evoked BOLD signal (Scheeringa et al. 2011). Finally, imperceptible stimulation itself has been shown to modulate cortical oscillatory activity (Balconi and Ferrari 2012; Bareither et al. 2014b; Nierhaus et al. 2015; Simon and Mukamel 2016; Forschack et al. 2017; Ten Oever et al. 2017).

For the somatosensory system, we face a similar set of findings. Amplitude of sensorimotor alpha rhythm, that is, mu rhythm, influences perception of somatosensory stimuli (Linkenkaer-Hansen et al. 2004; Zhang and Ding 2010; Weisz et al. 2014) and modulates late evoked potentials that are related to perceptual processing (Reinacher et al. 2009; Schubert et al. 2009). These findings already indicate that any external intervention, which modulates background alpha/mu rhythm, could alter somatosensory perception of an upcoming stimulus. Interestingly, we have recently shown that single subthreshold pulses lead to a transient mu rhythm increase (synchronization) over the contralateral pericentral region (Nierhaus et al. 2015). Previously, we had found that imperceptible pulse train stimulation impaired detection of intermingled near-threshold target stimuli and, furthermore, led to a negative BOLD response in contralateral primary somatosensory cortex (cS1; Blankenburg et al. 2003; Taskin et al. 2008), which in turn is probably related to cortical inhibition as shown in several other systems (Hamzei et al. 2002; Hlushchuk and Hari 2006; Shmuel et al. 2006).

Bringing these findings together, we assume that external stimulation, which modulates background alpha rhythm, would also alter perceptual performance. We hypothesize that changes in mu rhythm synchrony following subthreshold stimulation can be related to a psychophysically observable effect and thus might represent the underlying cortical mechanism. In this context, it was unclear to us whether the functional inhibition we reported for subthreshold train stimulation is simply the accumulation of single pulse repetition. In order to directly compare the two subthreshold stimulation conditions, that is, single pulses versus pulse trains, we performed a systematic study. Using electroencephalography (EEG), we investigated somatosensory evoked potentials (SEPs) and spectral alterations following subthreshold electrical finger nerve stimulation. In a complementary psychophysical approach, we measured perceptibility of target pulses (TPs) when combined with either subthreshold single pulses or pulse trains. By testing TPs delivered at different characteristic latencies—with respect either to the kinetics of cortical inhibition (Swadlow and Gusev 2000) or to the previously confirmed subthreshold effect on mu rhythm (Nierhaus et al. 2015)—we compare the effect of subthreshold pulses on the detection of targets that are delivered either after a preceding single pulse or delivered together with a subthreshold train. Specifically, we hypothesized that subthreshold trains would also increase mu-alpha synchronization—due to repetition possibly even stronger than a single pulse—and that both single pulses and brief trains would induce functional inhibition.

Materials and Methods

Subjects

We performed one EEG and six psychophysical experiments on a total of 158 participants (female, 84; male, 74; age range, 18–38 years). For EEG recordings, 40 healthy volunteers were recruited (mean age and standard deviation [SD] 28.6±2.8 years). Psychophysical measurements were performed independently in six separate experiments: A1: $n = 20$, 25.3 ± 2.7 years; A2: $n = 21$, 26.1 ± 2.9 years; A3: $n = 19$, 27.0 ± 2.6 years; B1: $n = 21$, 25.1 ± 2.3 years; B2: $n = 19$, 26.0 ± 2.8 years; B3: $n = 18$, 26.0 ± 2.8 years. All subjects were right handed with a mean laterality score of 89.0 ± 12.9 SD (within a range of −100 to +100, i.e., fully left and right handed, respectively, according to Edinburgh Handedness Inventory; Oldfield 1971). None of the subjects had a history of any neurological/psychiatric disorder or medication. Experiments were performed in accordance with the principles of the Declaration of Helsinki. Prior to participation, all volunteers gave written informed consent to participate in the experiment. This study was approved by the ethics committee of the University of Leipzig, Germany (Nr. 462/15-ek).

Electrical Finger Stimulation

For somatosensory stimulation, single monopolar square-wave current pulses (duration 200 µs) were delivered to the sensory nerves of the left index finger via steel-wire ring electrodes placed on the middle and proximal phalanx with the cathode located proximally (Fig. 1); the constant-current stimulator (DS series, Digitimer) was controlled by routines written in Matlab (Version R2017a, MathWorks) and Presentation (Neurobehavioral Systems). Prior to an EEG or psychophysics experiment, individual absolute detection threshold and respective stimulation amplitudes were assessed as previously described in detail (Nierhaus et al. 2015; Forschack et al. 2017). The absolute detection threshold is considered as the lowest current intensity for a continuous 7 Hz pulse train (0.1 mA steps) at which a subject was still able to report a sensation (method of constant stimuli). The current intensity for subthreshold single pulse and pulse train stimulation was set ~15% below the absolute detection threshold to ensure it is indeed reliably imperceptible throughout the entire experiment. This procedure was confirmed to provide undetectable stimulus intensities as we have previously demonstrated using a one-alternative forced choice detection task (Forschack et al. 2017).

EEG Acquisition

Thirty-two-channel EEGs (modified 10–20 system; reference FPz) were acquired with the BrainAmp amplifier/AD converter system and respective recording software (0.015–1 kHz band pass filter; sampling frequency, 5 kHz; Brain Products). The stimulation paradigm comprised two conditions where subthreshold single pulses and subthreshold pulse trains at 7 Hz (repetition of eight pulses; duration, 1 s) were delivered to the left

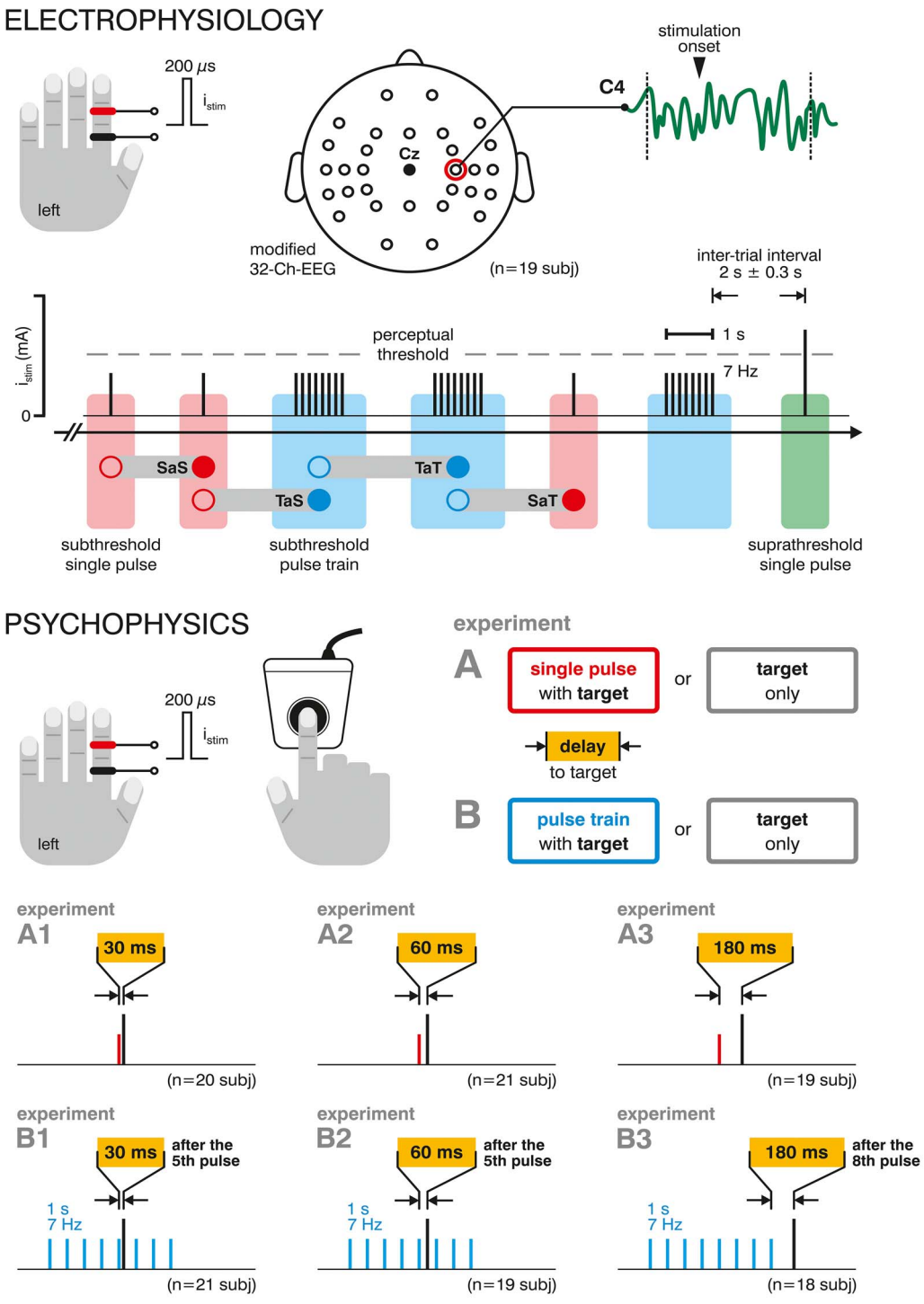

Figure 1. Schematic overview of experimental procedures. Electrophysiology: acquisition of an extended 32-channel EEG (40 subjects) during electrical nerve stimulation of the left index finger with subthreshold single current pulses (red), brief (1 s) subthreshold current pulse trains (eight pulses at 7 Hz, blue), as well as—to maintain attentional level—suprathreshold single pulses (*green*) in a pseudo-randomized order. Each subthreshold stimulation epoch was sorted offline according its pre-trial history (labeled, e.g., "single after train", SaT), that is, whether it was presented after a subthreshold single pulse or pulse train. C4 electrode signal time courses underwent preprocessing, segmentation, and averaging (SEPs) as well as TFA. Psychophysics: Subthreshold single pulse or pulse train (1 s at 7 Hz) stimulation was combined with presentation of near-threshold TPs at different delays (30 ms, 60 ms, and 180 ms), resulting in six different conditions that were compared to the control condition (i.e., TP presentation without any subthreshold stimulation) in separate experiments (A1 to A3 and B1 to B3). In experiments B4 and B5, the TP was delivered after the fifth subthreshold pulse of the train (i.e., embedded in the train). In experiment B3, the target was delivered 180 ms after the last subthreshold pulse. The paradigm drawings are displayed out of scale for illustration purposes. Subjects' responses were recorded (button press) in a simple detection task.

index finger in a pseudo-randomized order (mean interstimulus interval, 2 s; jitter, ±300 ms). The EEG paradigm contained 360 trials per either condition and was divided in 12 blocks (duration ~2.5 min) separated by brief pauses. After the sixth and the last block, the initially determined absolute detection thresholds were checked for potential drifts. Additionally, rarely interspersed low-intensity suprathreshold single pulses (four per block) on the left and right index finger were applied; subjects were instructed to count and report perceived pulses in each inter-block pause: with this instruction, we aimed to retain potential attentional fluctuation acceptably low and induced a level of attention comparable to the setting in the behavioral experiments. Furthermore, as EEG effects of subthreshold stimulation are subtle and therefore difficult to detect, the acquisition of suprathreshold SEPs serves as a kind of "internal calibration" to exclude systematic errors in the data acquisition or analysis overall. Electrode impedances were <5 kΩ throughout all measurements. Following our previous approach (Nierhaus et al. 2015; Forschack et al. 2017), we preselected electrode C4 (i.e., over pericentral region contralateral to stimulation site) for further analyses and statistical testing.

EEG Data Analyses

EEG data were analyzed off-line using custom-built Matlab scripts. Data were digitally filtered using a standard third order bandpass Butterworth filter (low cutoff frequency, 1 Hz; high cutoff frequency, 45 Hz). After downsampling to 500 Hz and concatenating all blocks, the data set of each subject underwent an independent component analysis (ICA) to remove sources of ocular artifacts (Li et al. 2006).

SEPs

An EEG segmentation analysis was performed on data obtained from electrode C4 as it captures signaling from the hand in area cS1/pericentral region most closely. For subthreshold stimulation, this is indicated by the P60 component as we have previously shown (Nierhaus et al. 2015; Forschack et al. 2017). Epochs were defined ranging from −200 to 2400 ms for subthreshold train stimulation trials. SEPs were obtained by averaging all trials or by averaging a subset of trials depending on the pre-trial history. To evaluate the P60 component, time points from 55 to 65 ms were averaged and compared to baseline (−200 to 0 ms) or between conditions in a paired *t*-test.

Rolandic Rhythms

Since Rolandic rhythms can be hidden under predominating occipital alpha activity, a preselection of "central" ICA components was performed before trial segmentation (Nierhaus et al. 2015; Forschack et al. 2017) in order to isolate and include only sources of Rolandic oscillatory activity that are related to somatosensory processing. Rolandic rhythms are characterized by a central localization and a power spectrum that exhibits two characteristic peaks, at alpha (7–14 Hz) and beta (15–29 Hz) frequency bands, respectively (Jones et al. 2009), which both desynchronize after suprathreshold stimulation. Based on this operational definition to identify Rolandic rhythms, for each subject only those components obtained by ICA were selected, for which the following criteria applied: 1) central topography, 2) the two respective peaks (alpha and beta) in the frequency spectrum, and 3) a desynchronization episode after suprathreshold stimulation. Consequently, two to seven (mean, 3 ± 1 SD) independent components were selected in each subject's data set, which were back-projected to the electrode space and segmented to subthreshold epochs as defined above. To allow for a time-resolved frequency analysis, a wavelet analysis for the frequencies from 4 to 30 Hz in 1 Hz increments was performed on single trial epochs using a five-cycle long wavelet. The resulting time-frequency data were finally averaged over trials of interest according to the corresponding stimulation condition. A 200 ms prestimulus epoch (−200 ms to 0 ms) was defined as baseline. For the time-frequency data, we used a nonparametrical cluster-based permutation test (Maris and Oostenveld 2007) with 1000 iterations: at the subject level, in each iteration, we permuted the mapping either between post-onset data points of the two conditions ("SaS" vs. "SaT"; Fig. 3B) or between post-onset data points and baseline values (Fig. 4A) and used a paired *t*-test at the group level to test each data point for significance (i.e., whether the signs were consistent). Then, we assessed the sum of *t*-values within largest contiguous cluster of significant time-frequency points (threshold $P < 0.05$), resulting in a distribution of *t*-value sums expected under the null hypothesis. Clusters in the observed data exceeding the family-wise error-corrected threshold (pFWE < 0.05) were considered to be statistically significant.

Psychophysical Experiments

In a simple detection task, subthreshold stimulation was combined with near-threshold stimulation (target) at one of three different delays with respect to the concomitant subthreshold event, i.e., either a single subthreshold pulse or a 7 Hz pulse train of eight pulses and 1 s duration (Fig. 1): In experiments A1 to A3, subthreshold single pulse stimulation was paired with a succeeding TP at an interpulse delay of 30, 60 (characteristic inhibition decay latencies; Swadlow and Gusev, 2000), and 180 ms (subthreshold effect on EEG rhythm; Nierhaus et al. 2015); for concomitant subthreshold pulse train stimulation, the TP was applied either within the train (trials resembling continuous subthreshold stimulation; Taskin et al. 2008) after the fifth pulse at a delay of 30 or 60 ms (experiments B1 and B2) or after the entire pulse train, with a delay of 180 ms (experiment B3). Each of these conditions was tested independently in separate experiments (Fig. 1; experiments A1 to A3 and B1 to B3) on different groups of subjects. Prior to an experiment, the subthreshold stimulation intensity was determined following the procedure described above. Each experimental block started with a staircase procedure to determine the individual 50% detection threshold, by which five linearly increasing near-threshold intensities were set as TP intensities. A single experiment consisted of three blocks (~9 min duration each) and comprised two types of trials: Presentation of TP only (control) and TP with concomitant subthreshold stimulation; in a single block, each TP intensity was repeated 32 times, while in half of the trials (i.e., 16 per intensity), the TPs were accompanied by subthreshold stimulation. Subjects were instructed to press a button (right index finger) as fast as possible whenever they detected a stimulus. This simple detection task allows no comparison between changes in sensitivity versus criterion (according to signal detection theory [SDT]). We nevertheless chose this design in order to minimize attentional shifts and visuo-cognitive interaction by monitor-displayed instructions that would likely "overshadow" the weak effects elicited by the subthreshold stimuli in the EEG experiment. To overcome this limitation, a much longer EEG experiment would have been required to obtain enough signal

to noise for these small signals. Such a prolonged paradigm, however, would be of nonfeasible duration with additional unpredictable time-dependent contaminative effects (e.g., habituation or attentional shifts). Although this design ensures certain similarity of the behavioral and EEG experimental design, the comparison of the resulting effects induced by subthreshold stimulation has to be interpreted with caution due to the still existing discrepancies. Catch trials containing only subthreshold stimulation (16 per block) were additionally included to control for the stimulus' imperceptibility; a subject's data would be discarded if a button response was given to more than one catch trial (in a total of 354 recorded blocks this occurred only in two blocks for different subjects). For statistical analysis, in each of the six psychophysical experiments, the individual detection rates for the test and control conditions were averaged and compared using a paired *t*-test. Changes in detection performance are reported as relative changes to the respective control condition (trials containing only TPs), that is, $(\text{rate}_{\text{condition}} - \text{rate}_{\text{control}})/\text{rate}_{\text{control}}$.

Results

Subthreshold Single Pulse Stimulation: SEPs and TFA

Subthreshold single pulse stimulation elicited a weak (in comparison to the suprathreshold pulse; Fig. 2A) voltage response (grand average) containing a single discernible (i.e., statistically significant) positive component at a peak time ~60 ms, the P60 [Fig. 2A; mean amplitude of the 55 to 65 ms poststimulus interval vs. baseline, $t(39) = -2.7399$, $P = 0.0092$], thus confirming our recent finding (Nierhaus et al. 2015; Forschack et al. 2017). Consequently, we would have also expected to find an event-related synchronization in the mu-alpha band as described in our above-mentioned studies. However, the absence of a similar spectral alteration in the present EEG data (Fig. 3A) as well as previous findings concerning the impact of past trial history for behavioral data (Thiel et al. 2014) enforced the assumption that processing in cS1 associated with the preceding trial (i.e., subthreshold single pulse or pulse train stimulation) might still interfere with the cortical response to the very succeeding stimulation event. To control for a potential history trial-related hysteresis effect, we sorted EEG epochs with regard to the previous trial condition "single pulse" or "pulse train" stimulation, which were labeled "SaS" (single pulse after single pulse) and "SaT" (single pulse after pulse train), respectively. The resulting grand SEPs both exhibited a respective component within the P60 window [Fig. 2; SaS: $t(39) = -2.0434$, $P = 0.0478$; SaT: $t(39) = -2.143$, $P = 0.0384$], being not significantly different [SaS vs. SaT: $t(39) = 0.0484$, $P > 0.9$].

When sorting the single pulse time-frequency analyses (TFAs) according to the past trial, we observe differential changes in the alpha frequency band: When averaging only the events following single pulse stimulation (SaS; Fig. 3B), a synchronization pattern emerges ~200 ms after stimulus onset and continues up to >300 ms (similar to what we have initially expected based on our previous studies; Nierhaus et al. 2015; Forschack et al. 2017), whereas trials following subthreshold train stimulation (SaT; Fig. 3B) are associated with a poststimulus desynchronization from ~250 to >300 ms. While these desynchronization/synchronization patterns are not significant versus baseline alpha power, the contrast between the sorted TFA conditions (SaS versus SaT) shows a significant cluster (FEW-corrected $P < 0.041$; Fig 3B, right panel). The time-frequency window for the statistical comparison was set according to our a priori hypothesis derived from our previous findings (Nierhaus et al. 2015).

Subthreshold Train Pulse Stimulation: SEPs and TFA

In the grand average SEP obtained for subthreshold pulse train stimulation, the initial P60 component of the first intra-train pulse was not significant compared to baseline [Fig. 2B; $t(39) = -1.234$, $P > 0.2$], yet still shows a similar shape and matching latency as for the subthreshold single pulse [Fig. 2B; red overlay, no significant amplitude difference, $t(39) = -1.489$, $P > 0.14$]. For the subsequent pulses, no clear latency pattern was observed (except for a biphasic potential between the third and fourth pulse of unclear relevance). After pre-trial sorting, we find that trains following single pulses (TaS) exhibit a significant initial P60 deflection [precomponent time segment vs. P60, i.e., 38–42 ms vs. 66–70 ms; $t(39) = -2.313$; $P = 0.0261$]; however, for trains after trains (TaT), there is no discernible P60 [precomponent time segment vs. P60, $t(39) = -0.729$; $P > 0.4$]. It seems that strong baseline fluctuations were critical to significantly detect the (subtle) initial P60 component for train stimulation.

Subthreshold train stimulation induced a marked desynchronization of ongoing mu-alpha activity (Fig. 4A), being statistically significant (lower panel; nonparametrical cluster FWE-corrected $P = 0.044$); desynchronization started to evolve ~100 ms after stimulation onset and further increased with succeeding pulses. During train stimulation, for a brief episode, desynchronization appeared also in the beta frequency band. The alpha desynchronization continued beyond the end of the pulse train for ~1 s (i.e., persists after stimulation offset). Thereafter, a subsequent short increase of synchrony in the beta frequency band can be observed ("beta rebound"; statistically not significant). After pre-trial sorting, respective TFAs both showed mu rhythm desynchronization; however, for successive train stimulation (TaT), desynchronization emerged earlier and continued for a considerably longer time (>2 s) as compared for the single pulse pre-trial condition (TaS; Fig. 4B). The maintenance of the desynchronized state is also supported by the desynchronization induced by single pulse stimuli that follow pulse trains (SaT; Fig. 3B), that is, although subthreshold single pulse stimulation is associated with an increase in the amplitude of mu-alpha (Fig. 3B), a pulse train persistently shifts network dynamics so that a following single pulse is enough to reinduce desynchronization. In other words, the dominant persisting alpha desynchronization induced by the repetitive stimulation is responsible for the absence of mu-alpha synchrony when averaging over all single pulse trials (Fig. 3A).

Psychophysics: Impact of Subthreshold Stimulation on TP Detection

We complemented the electrophysiological study with psychophysical experiments where we investigated changes in perceptibility of near-threshold TPs when paired with a subthreshold single pulse or a subthreshold pulse train at different delays (Fig. 1). For a delay of 60 ms, subthreshold single pulse stimulation led to a significant increase of mean TP detection rate by 6.5% [Fig. 5; relative to target only; $t(20) = 2.6545$, $P = 0.0152$]. For the delays 30 and 180 ms, no significant effect on TP detection was found [$t(19) = -0.5106$, $P > 0.615$

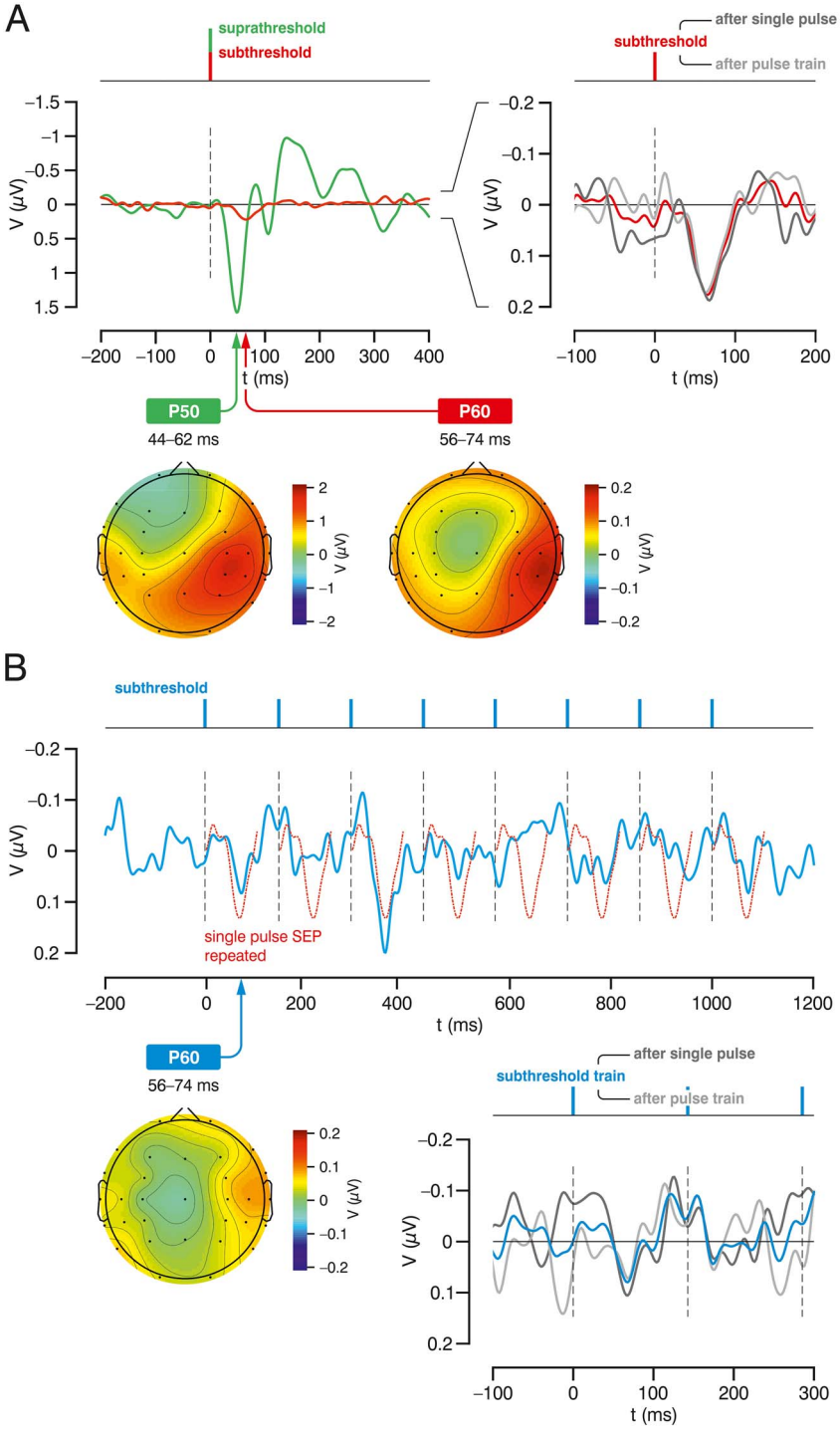

Figure 2. SEPs. (*A*) Grand average SEPs (40 subjects) in response to single pulse stimulation on the left index finger. Left: subthreshold (red) SEP confirming the characteristic P60 component; suprathreshold SEP (green). Right: SEPs for subthreshold stimulation sorted according pre-trial history (SaS and SaT; dark and light gray, respectively), both comprising a P60 component (no significant difference). Below: topographic maps of the P50 and P60 component for supra- and subthreshold single pulse stimulation, respectively. (*B*) Grand average (blue) for subthreshold train stimulation with presumable initial pulse-related component but lacking consecutive train-driven synchronicity (dotted red: single pulse-SEP shown in Fig. 2A drawn repetitively as a ''pseudo-phase-locked'' response to each pulse of the train for comparison); bottom right: grand average SEPs for subthreshold train stimulation (initial part) sorted according to pre-trial history (train, TaS, and TaT; blue, dark, and light gray, respectively); bottom left: topographic map of the initial P60 component in response to subthreshold train stimulation.

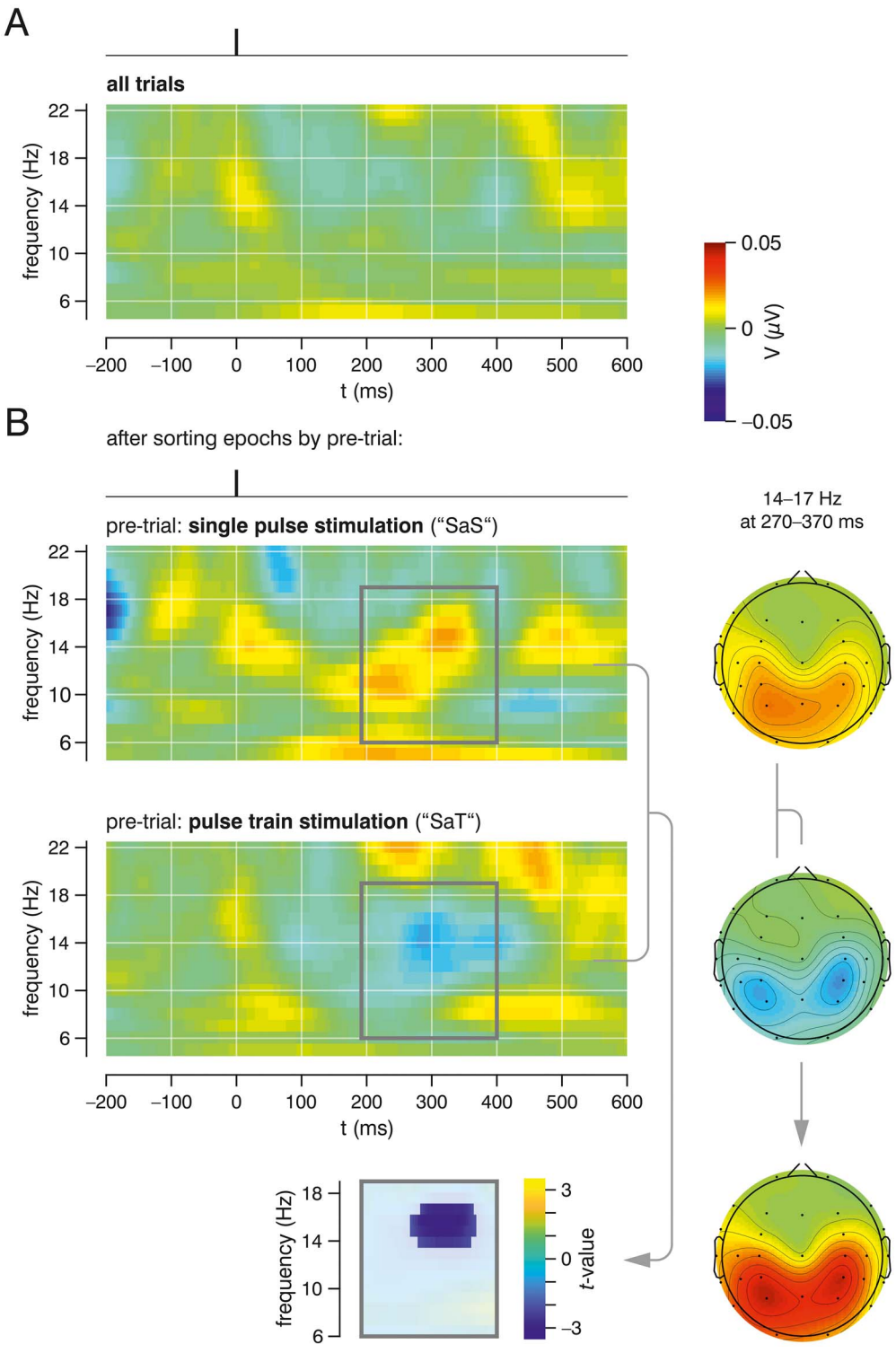

Figure 3. TFA for subthreshold single pulse stimulation. (*A*) Average from all trials does not show any significant change in EEG frequency spectrum. (*B*) Averages from respective trials after pre-trial sorting: "single pulse after single pulse" (SaS, upper panel) and "single pulse after pulse train" (SaT, lower panel). Bottom: Nonparametric statistical analysis (contrasting SaS vs. SaT) reveals a significant cluster according to the expected rhythm change at ~200 ms poststimulus. The window for statistical comparison was chosen a priori based on previous findings (Nierhaus et al. 2015). Right column: topographic maps of the significant cluster (14–17 Hz, 270–370 ms; as determined by the above-mentioned nonparametric test) for SaS and SaT conditions, as well as their difference (for illustration purposes only, without statistical testing).

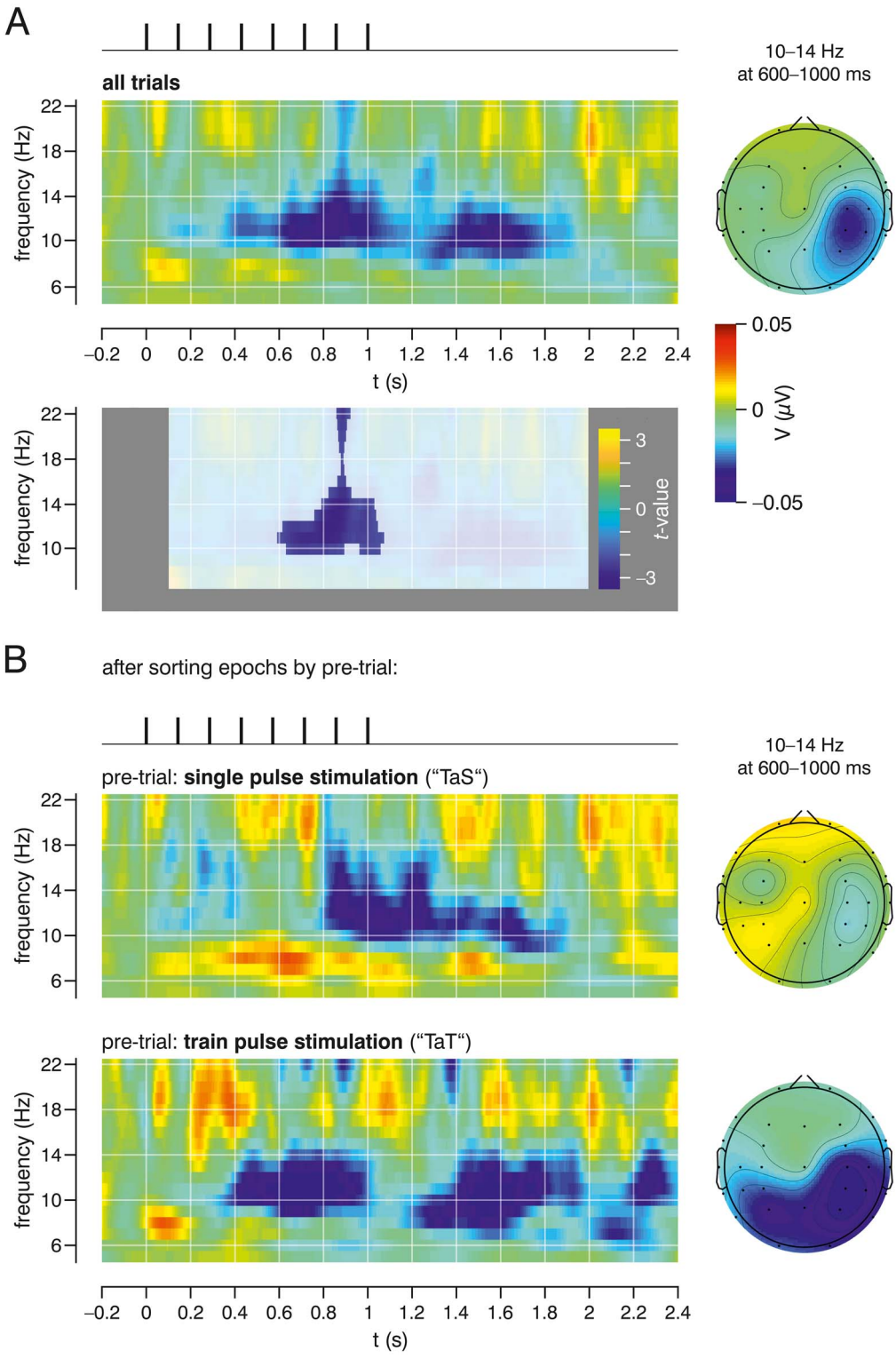

Figure 4. TFA for subthreshold pulse train stimulation. (*A*) Average from all subthreshold train stimulations (unsorted trials; upper panel). In the nonparametric statistical analysis (comparison of the 100 ms–2 s window against baseline, i.e., –200 ms to 0 ms; lower panel), a single significant cluster (inlay) is specified. (*B*) TFAs for subthreshold pulse train stimulation after pre-trial sorting: "train after single pulse" (TaS, upper panel) and "train after train" (TaT, lower panel). Both show a decrease in the mu-alpha range emerging during train stimulation and lasting for ~1 s after (not significant in cluster analysis). Right: Topographic maps of the significant cluster (10–14 Hz, 600–1000 ms; as determined by the nonparametric test in *A*) for all trials and after pre-trial sorting (TaS and TaT).

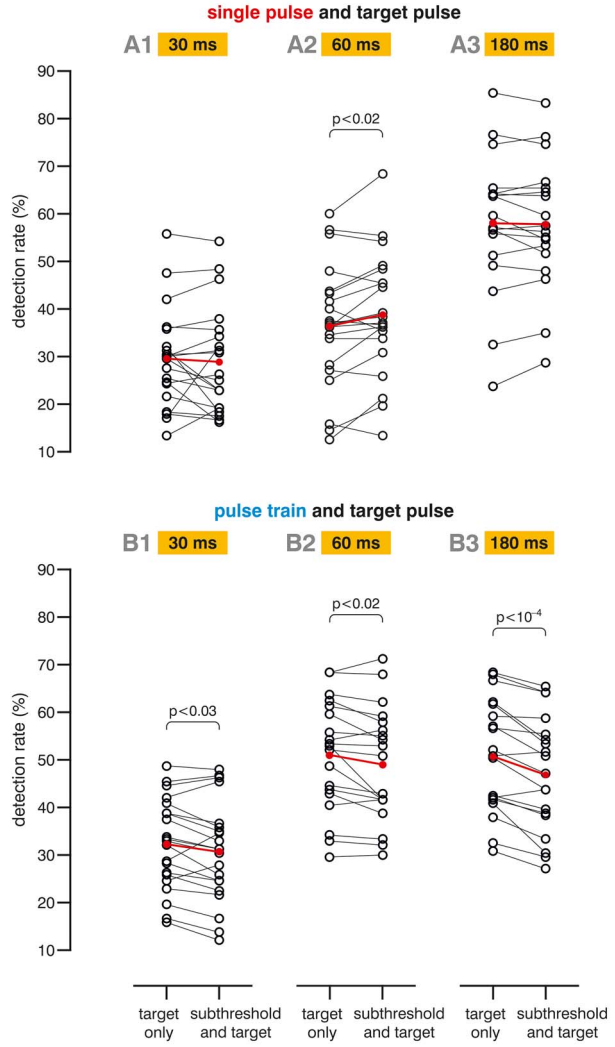

Figure 5. Psychophysical performance. Detection rates obtained in six separate experiments (A1 to A3 and B1 to B3; as described in Fig. 1). Upper panel: Subthreshold single pulse stimulation was associated with an increase of mean detection rate by 6.5% (relative change, i.e., as compared to the target only condition) for a delay of 60 ms between near-threshold TP and preceding subthreshold single pulse; for the other delays (30 and 180 ms), no significant change was found. Lower panel: Subthreshold pulse train stimulation induced a significant decrease in mean TP detection rates for all tested delays, by 5.0%, 3.9%, and 7.7% (relative changes) for a delay of 30, 60 (after the fifth pulse of the train, respectively), and 180 ms (after end of the train).

and $t(18) = -0.7159$, $P > 0.482$, respectively]. In contrast, with concomitant subthreshold pulse train stimulation, mean TP detection rates were reduced for all delays tested: by 5.0% for 30 ms [$t(20) = -2.4025$, $P = 0.0261$], by 3.9% for 60 ms ($t(18) = -2.5993$, $P = 0.0181$), and by 7.7% for 180 ms [$t(17) = 5.1942$, $P < 10^{-4}$].

Discussion

We performed somatosensory subthreshold (i.e., imperceptible) single pulse and pulse train stimulation to look for its EEG signatures and examined its impact on perceptibility of near-threshold TPs. The comparison of subthreshold single pulse stimulation between conditions of different preceding stimulus (SAS vs. SAT) disclosed a transient pattern of increased mu-alpha synchronization for subthreshold single pulses following single pulses (~150 to ~300 ms after stimulation), similar to what we expected based on our previous studies. Conversely and being a novel finding, repetitive subthreshold stimulation led to a prolonged mu-alpha desynchronization evolving ~400 ms after train onset and outlasting the train at least 800 ms. Interestingly, the modulatory effect of subthreshold train stimulation even exceeded the period of desynchronization, since mu-alpha activity of subsequent trials was still affected (e.g., mu-alpha synchronization was absent when the single pulse followed a previous train stimulation). In psychophysics, subthreshold train stimulation (1 s at 7 Hz) decreased perceptibility of near-threshold TPs at all tested delays (30, 60, and 180 ms). In contrast, single subthreshold pulses either enhanced detection of TPs (at 60 ms delay) or had no significant effect (at delays of 30 and 180 ms, respectively).

Single subthreshold pulse stimulation evoked a P60 component (together with mu-alpha synchronization) confirming central processing of subthreshold stimulation (Nierhaus et al. 2015; Forschack et al. 2017). For subthreshold train stimulation, a P60 deflection related to the initial pulse of the train was detected while subsequent phase- or stimulus-locked deflections were missing, that is, no stimulus-driven oscillations in terms of rhythm entrainment were observed. Notably, the P60m component of somatosensory evoked fields in response to median nerve stimulation has previously been shown to vanish at a repetition time of 150 ms (i.e., at ~7 Hz, though this occurred under steady-state conditions; Wikström et al. 1996).

In previous studies, we already demonstrated that subthreshold electrical finger nerve stimulation elicited a negative BOLD response in cS1 and moreover diminished the positive BOLD response to suprathreshold stimulation (Blankenburg et al. 2003; Taskin et al. 2008). A negative BOLD signal change from baseline ("fMRI deactivation") is assumed to mirror a suppressed state of cortical activity and was repeatedly attributed to indirectly reflect synaptic inhibition in different systems (e.g., Gusnard and Raichle 2001; Hamzei et al. 2002; Hlushchuk and Hari 2006; Shmuel et al. 2006). Furthermore, we previously reported an impeding effect of sustained subthreshold train stimulation (20 s) on TP detection (Blankenburg et al. 2003; Taskin et al. 2008). Following these previous studies, we here chose again the "simple detection task" because the subtle behavioral and EEG changes following subthreshold stimulation would be difficult to detect when superimposed by large attention- and visuomotor-related effects induced in an SDT-based design. We now show that brief subthreshold pulse trains of 1 s duration are already sufficient to elicit this functional inhibition. We regard the low intensity of subthreshold stimulation to be crucially responsible for the inhibitory effects we observe. This is strongly supported by various in vivo and in vitro experiments on thalamocortically mediated feedforward inhibition in cS1: Inhibitory interneurons of somatosensory barrel cortex were found to have considerably lower excitation thresholds than principal neurons (Swadlow 1995; Gil and Amitai 1996; Swadlow and Gusev 2000). Thus, the weak subthreshold stimulation in our experimental design is more likely to selectively activate a larger population of cortical inhibitory interneurons. As for the kinetics of synaptic inhibition, inhibitory postsynaptic potentials (IPSPs) in the targeted pyramidal cells (elicited disynaptically via local inhibitory interneurons) exhibited a peak at ~30 ms and decayed within another 30 ms (Swadlow and Gusev 2000). Accordingly, in the psychophysical experiments,

we time-locked TPs to subthreshold stimulation at 30 and 60 ms. Driven by our finding of mu-alpha synchronization (as outlined below putatively resembling lowered cortical excitability), we additionally tested a delay at which we would expect interaction of TP-related processing with oscillatory activity induced by preceding subthreshold stimulation (maximum at ~200 ms; by choosing 180 ms, we have taken into account a latency of ~20 ms until peripheral stimulation reaches cS1). Consequently, for the single pulse condition, we anticipated target detection would be impaired at the maximum of the IPSP (30 ms) as well as during the mu-alpha increase (180 ms), whereas at the low state of inhibition (60 ms, late decay phase) detection would remain unchanged. Surprisingly, no detection impairment was seen for the 30 and 180 ms delays, while at 60 ms a facilitation occurred. Possibly, time locking the TP to the IPSP decay phase results in noise reduction as compared to random target presentation in the control condition. Another critical parameter for the paired pulse detection might be the rhythmical modulation of perception driven by the subthreshold stimulus. While the model of perceptual cycles was not developed based on mere detection but on time discrimination tasks (Baumgarten et al. 2017), the rhythmical modulation of discreet cycles in the beta band (13–18 Hz) might also contribute to the selective detection enhancement of TPs falling in the respective time window (55–77 ms). This is also in line with the model we discussed above, according to which the duration of each perceptual cycle is defined at the cellular level (decay of inhibition). A single subthreshold pulse is probably not sufficient to elicit a psychophysically measurable inhibitory effect at the other delays. The claim that synaptic inhibition is indeed enhanced by subthreshold stimulation is still supported by the impaired perceptual performance due to repetitive stimulation (train).

How do subthreshold stimulation and inhibition relate to oscillatory activity in cS1? Fundamental determinants of mu rhythm generation and modulation are: 1) thalamocortical excitation of cortical pyramidal cells and cortical feedback within the thalamocortical loop (the traditional view of driving pacemaker function of thalamus), 2) feedforward and feedback inhibition of principal neurons via the intracortical interneuron network, and, eventually, 3) massive context-dependent and task-related top-down projections, for example, from motor cortex and various other frontal areas (Swadlow and Gusev 2001; Klimesch et al. 2007; Miller et al. 2007; Bollimunta et al. 2011; Neske et al. 2015). For instance, simulation of the above-mentioned actors in a columnar S1 model sufficiently reproduced magneto-encephalographic data on humans (Jones et al. 2009). In our study, the implementation of subthreshold stimulation serves as an experimental tool to selectively investigate the role of intracortical inhibitory interneuron networks in mu rhythm modulation. The imperceptibility of the stimulation and the task-free paradigm jointly ensure that afferent input processing does not entail conscious—in our case "confounding"—perception-related processes such as expectation, motor preparation and response, attentional focusing, or habituation, which is frequently observed in the context of supraliminal stimulation.

We demonstrate that subthreshold stimulation modulates mu-alpha activity; however, single pulses and pulse trains exert opposite effects: Confirming our previous findings (Nierhaus et al. 2015; Forschack et al. 2017), alpha synchronization is induced after consecutive single pulses, whereas desynchronization emerges after pulse trains. Alpha activity has been frequently linked to inhibition (Jensen and Mazaheri 2010; Klimesch et al. 2007). For the visual system, it has been shown that higher alpha power in posterior regions correlates with lower detection rates of visual stimuli (Ergenoglu et al. 2004; Babiloni et al. 2006; Hanslmayr et al. 2007; van Dijk et al. 2008). Similarly, for the somatosensory system, endogenous prestimulus alpha power has been shown to influence perception (Schubert et al. 2009). While these studies focus on the functional relevance of spontaneously fluctuating (endogenous) background rhythms, we have previously suggested that exogenous modulation of background rhythms might mediate the effect of subthreshold stimulation on target detection (Bareither et al. 2014b; Nierhaus et al. 2015). Following this notion, we expected detection impairment for a target stimulus delivered within the period of increased alpha power (~150 to ~250 ms) induced by subthreshold single pulse stimulation. However, no detection impairment was observed for any of the three delays tested.

Repetitive application of the same subthreshold stimulus no longer increases mu-alpha activity; instead, a long-lasting desynchronization is observed. Different from mere event-related desynchronization, consistently observed for suprathreshold stimulation (Neuper et al. 2006), we assume that during subthreshold train stimulation the induction of synchronization by the first subthreshold "single" pulse is conflicted by signal processing associated with the subsequent subthreshold pulses: Synchronization should occur ~200 ms after the initial subthreshold pulse. However, the succeeding intra-train stimuli at the pulse period of ~140 ms (7 Hz) prevent this process to evolve; instead, the repetitive input leads to mu-alpha desynchronization. Moreover, subthreshold train stimulation consistently leads to a decrease of TP detection regardless of the time delay to the preceding subthreshold pulse. Each tested delay falls into the period of desynchronization, but only the 180 ms is well beyond the decay phase of synaptic inhibition. Consequently, we regard train-induced detection decrease for late presented target stimuli as a convincing link between mu-alpha desynchronization and inhibitory interneuron activity. The desynchronization that we observe, however, is not equivalent to reduced alpha power as it occurs in endogenous alpha fluctuations, as discussed above. Rather, our results indicate that an altered state of cortical processing induced by the pulse train persists at least ~2 s beyond stimulation. Consistent with this notion, we find a divergent effect of single pulses after controlling for pre-trial history (i.e., hysteresis): By contrasting SaS versus SaT, we disclosed a significant difference between the single pulse trials depending on the previous trial stimulation. While SaT tends to decrease alpha synchrony, SaS seems rather associated with a transient mu-alpha increase similar to the one previously reported (Nierhaus et al. 2015; Forschack et al. 2017). Still, only the contrast of the two conditions was statistically significant but not the power change versus baseline. This may be due to low statistical power after trial sorting and thus have to be confirmed by future studies. It is known that representations of task- or stimulus-related information can persist in the absence of stimulation in patterns of synaptic weights (Jonides et al. 2008). The considerably long persistence of train-induced desynchronization together with the hysteresis effect suggests a persistent shift in cortical excitation-inhibition balance (Isaacson and Scanziani 2011), where also mechanisms in synaptic plasticity can play a role. This is why a single subthreshold pulse can still reinforce the fading desynchronization. By design, however, the stimulus

history effects cannot be directly translated from the EEG to the behavioral experiments and any correlation or interpretation of the behavioral data with the EEG data should be taken with caution. Nevertheless, our approach of implementing the same stimuli in separate experiments allows one to bring the electrophysiological and behavioral correlates together, which in turn will help to design combined EEG/behavioral paradigms addressing more detailed questions.

In conclusion, a single subthreshold pulse elicits mu-alpha synchronization but is not sufficient to exert measurable functional inhibition. Its sole repetition, however, progressively shifts the cortical excitation-inhibition balance toward a robust cortical inhibitory state that persistently affects subsequent stimulus processing and is paralleled by prolonged mu-alpha desynchronization. Evidently, the inhibitory component associated with subthreshold stimulation becomes functionally relevant only through repetition. Beyond the established notion of increased alpha activity acting as a mediator of functional inhibition, we demonstrate that it is possible to generate a cortical state of increased inhibition accompanied by mu-alpha desynchronization. Our findings offer a new approach for controlled nonconscious, noncognitive, and attention-independent manipulation of cortical synchrony and excitability in opposite directions.

Notes

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Publication 3

Al E, **Iliopoulos F**, Forschack N, Nierhaus T, Grund M, Motyka P, Gaebler M, Nikulin VV, Villringer A. Heart-brain interactions shape somatosensory perception and evoked potentials. Proc Natl Acad Sci U S A. 2020. 117(19):10575-10584

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1	NATURE	745,692	43.070	1.285010
2	SCIENCE	680,994	41.037	1.070190
3	National Science Review	1,842	13.222	0.006500
4	Science Advances	21,901	12.804	0.110010
5	Nature Communications	243,793	11.878	1.103290
6	Nature Human Behaviour	1,230	10.575	0.006550
7	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	661,118	9.580	1.022190
8	Science Bulletin	3,569	6.277	0.009840
9	Scientific Data	3,240	5.929	0.015610
10	Frontiers in Bioengineering and Biotechnology	1,994	5.122	0.006540
11	Journal of Advanced Research	2,691	5.045	0.004780
12	Research Synthesis Methods	1,932	5.043	0.005420
13	GigaScience	2,674	4.688	0.012510
14	Annals of the New York Academy of Sciences	46,385	4.295	0.025840
15	Scientific Reports	302,086	4.011	1.061540
16	Journal of the Royal Society Interface	12,933	3.224	0.029190
17	NPJ Microgravity	203	3.111	0.000670
18	PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A-MATHEMATICAL PHYSICAL AND ENGINEERING SCIENCES	19,227	3.093	0.028200

Original publication of study 3

Correction

NEUROSCIENCE

Correction for "Heart–brain interactions shape somatosensory perception and evoked potentials," by Esra Al, Fivos Iliopoulos, Norman Forschack, Till Nierhaus, Martin Grund, Paweł Motyka, Michael Gaebler, Vadim V. Nikulin, and Arno Villringer, which was first published April 27, 2020; 10.1073/pnas.1915629117 (*Proc. Natl. Acad. Sci. U.S.A.* **117**, 10575–10584).

The authors note that an additional affiliation should be listed for Esra Al, Fivos Iliopoulos, and Arno Villringer. The new affiliation should appear as Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin Berlin, 10117 Berlin, Germany. The corrected author and affiliation lines appear below. The online version has been corrected.

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Heart–brain interactions shape somatosensory perception and evoked potentials

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Even though humans are mostly not aware of their heartbeats, several heartbeat-related effects have been reported to influence conscious perception. It is not clear whether these effects are distinct or related phenomena, or whether they are early sensory effects or late decisional processes. Combining electroencephalography and electrocardiography, along with signal detection theory analyses, we identify two distinct heartbeat-related influences on conscious perception differentially related to early vs. late somatosensory processing. First, an effect on early sensory processing was found for the heartbeat-evoked potential (HEP), a marker of cardiac interoception. The amplitude of the prestimulus HEP negatively correlated with localization and detection of somatosensory stimuli, reflecting a more conservative detection bias (criterion). Importantly, higher HEP amplitudes were followed by decreases in early (P50) as well as late (N140, P300) somatosensory-evoked potential (SEP) amplitudes. Second, stimulus timing along the cardiac cycle also affected perception. During systole, stimuli were detected and correctly localized less frequently, relating to a shift in perceptual sensitivity. This perceptual attenuation was accompanied by the suppression of only late SEP components (P300) and was stronger for individuals with a more stable heart rate. Both heart-related effects were independent of alpha oscillations' influence on somatosensory processing. We explain cardiac cycle timing effects in a predictive coding account and suggest that HEP-related effects might reflect spontaneous shifts between interoception and exteroception or modulations of general attentional resources. Thus, our results provide a general conceptual framework to explain how internal signals can be integrated into our conscious perception of the world.

consciousness | somatosensory awareness | body–brain interaction | EEG | rhythms

The neural response to an external stimulus and its access to consciousness depend on stimulus features as well as the state of the brain (1–5). Interestingly, functional states of other bodily organs, such as the heart, can also influence the perception of external stimuli. For example, several studies have reported that timing along the cardiac cycle (e.g., systole vs. diastole) impacts the perception of visual or auditory stimuli (refs. 6 and 7, but also see refs. 8 and 9 for nonsignificant heart phase-dependent effects). For the somatosensory system, we recently showed increased detection during diastole (10) similar to the other sensory domains (6, 7). Interestingly, a previous study had reported lower somatosensory sensibility during diastole (11) when stimulus presentation was at fixed time points during the cardiac cycle. Similar to perception, neural responses to visual and auditory stimuli are modulated across the cardiac cycle (12, 13). Most often they have been reported to be higher during diastole than systole (12, 13). A recent study (14) has also associated fluctuations of the heartbeat-evoked potential (HEP; refs. 15–17) with conscious detection of a visual stimulus.

While thus increasing evidence indicates that events related to cardiac function may modulate conscious perception, fundamental questions remain unanswered. Is it perceptual discrimination ability, that is, sensitivity in signal detection theory (SDT; ref. 18), that is influenced by cardiac activity? Or, might a bias to report the presence or absence of a stimulus underlie the effect, that is, criterion, in SDT? Are criterion-free decisions also affected by the heart? How are these perceptual effects reflected in evoked neural activity? More specifically, do these effects influence early, preconscious, somatosensory-evoked potentials (SEPs) or only the late components? Ultimately, how cardiac-related modulation of perceptual awareness relates to primary determinants of sensory perception and evoked brain activity, such as prediction, attention, and background neural activity, is unknown.

The current study targets mechanisms linking heart, brain, and perception using a somatosensory detection and localization task with electroencephalography (EEG) recordings. In an SDT-based design, we identify differential effects of two heartbeat-related phenomena: 1) stimulus timing during the cardiac cycle

Significance

Our brain continuously receives signals from the body and the environment. Although we are mostly unaware of internal bodily processes, such as our heartbeats, they can affect our perception. Here, we show two distinct ways in which the heartbeat modulates conscious perception. First, increased heartbeat-evoked neural activity before stimulation is followed by decreased somatosensory detection. This effect can be explained by subjects adopting a more conservative decision criterion, which is accompanied by changes in early and late somatosensory-evoked responses. Second, stimulus timing during the cardiac cycle affects sensitivity but not criterion for somatosensory stimuli, which is reflected only in late somatosensory-evoked responses. We propose that these heartbeat-related modulations are connected to fluctuations of interoceptive attention and (unconscious) predictive coding mechanisms.

Author contributions: E.A., F.I., and A.V. designed research; E.A. and F.I. performed research; E.A., N.F., V.V.N., and A.V. analyzed data; and E.A., N.F., T.N., M. Grund, P.M., M. Gaebler, V.V.N., and A.V. wrote the paper.

The authors declare no competing interest.

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and 2) the amplitude of the HEP on somatosensory perception and evoked potentials. We argue that these findings are in line with a predictive coding account for cardiac phase-related sensory fluctuations and likely to be related to spontaneous shifts between interoception and exteroception as indexed by the HEP amplitude.

Results

Thirty-seven participants were presented weak somatosensory (electrical) stimuli to either the left index or middle finger in a combined yes/no detection and location discrimination task (Fig. 1). Both EEG and electrocardiography (ECG) were recorded. On average, participants detected 51.0 ± 10.5% (mean ± SD) of the somatosensory stimuli with a false alarm rate of 8.4 ± 7.7%. This corresponds to a mean detection sensitivity, d', of 1.57 ± 0.57 and a decision criterion, c, of 0.76 ± 0.32. Participants correctly localized 73.3 ± 6.6% of stimuli (fingerwise), corresponding to a mean localization sensitivity of 0.90 ± 0.32. Participants correctly localized 88.9 ± 7.9% of hits and 57.0 ± 6.9% of misses.

Detection Varies across the Cardiac Cycle. We hypothesized that hits were more likely to occur in a later phase of the cardiac cycle, whereas misses would occur in an earlier phase (10). We used three complementary approaches to test this hypothesis. First, we used circular statistics (19), which allows an assessment of the entire cardiac cycle, without distinguishing systole and diastole, whose relative lengths are differentially affected by changes in the duration of the cardiac cycle (see *Circular Analysis* for details). A Rayleigh test showed that hits were not uniformly distributed, $\overline{R} = 0.40$, $P = 0.003$ (Fig. 2*A*), with a mean angle of 308.70° corresponding to the later cardiac cycle phase (i.e., diastole). Similarly, the distribution of misses was not uniform, $\overline{R} = 0.40$, $P = 0.004$ (Fig. 2*A*), with a mean angle of 93.84°, located in the early phase of the cardiac cycle (i.e., systole). We observed a trend in the distribution of correct localizations toward the later phases of the cardiac cycle ($\overline{R} = 0.28$, $P = 0.067$). The distribution of wrong localizations was not significantly different from a uniform distribution, $\overline{R} = 0.17$, $P = 0.35$ (Fig. 2*A*).

Detection Rate and Sensitivity Are Higher during Diastole Compared to Systole. To account for the biphasic nature of the cardiac cycle, we also examined detection and localization performance by segmenting each cardiac cycle into systole and diastole: We operationalized the systolic time window for each cardiac cycle as the time between the R-peak and the end of the t-wave (see *Binary Analysis* for further details). Based on the duration of this systolic window, we defined a diastolic window of equal length at the end of each cardiac cycle (Fig. 2*B*). As suggested by our first analysis, the detection rate for the weak stimuli was significantly higher during diastole (mean [M] = 52.41%) than systole (M = 49.53%), $t_{36} = -3.95$, $P = 3{\cdot}10^{-4}$ (Fig. 2*B*). Increased detection rate during diastole was observed for 27 out of 37 participants. However, the false alarm rate did not differ significantly between systole (M = 8.50%) and diastole (M = 8.19%), $t_{36} = 0.54$, $P = 0.59$. There was no significant difference between stimulus intensities in systole and diastole ($t_{36} = 0.57$, $P = 0.57$; *SI Appendix*, Table S1). Additionally, we tested whether the latency to response differed between systole and diastole but did not find a significant difference ($t_{36} = 0.83$, $P = 0.41$).We furthermore tested whether the effect of cardiac phase on detection correlated with the heart rate or the heart rate variability (HRV, i.e., the SD of time duration between two successive R-peaks [RR intervals]) of individuals. While there was no significant correlation between subject's heart rate and their detection rate variation between systole and diastole (Pearson's correlation, $r = 0.01$, $P = 0.95$), subjects' HRV negatively correlated with their detection rate difference ($r = -0.36$, $P = 0.03$; *SI Appendix*, Fig. S1).

SDT was applied to test whether the increased detection rates in diastole were due to increased perceptual sensitivity (d') or due to adopting a more liberal response strategy (criterion). Detection sensitivity was significantly higher in diastole (M = 1.59) than systole (M = 1.48), $t_{36} = -2.38$, $P = 0.008$ (Fig. 2*B*). For the criterion, no significant difference between systole (M = 0.75) and diastole (M = 0.73) was found, $t_{36} = 0.71$, $P = 0.48$. Localization performance was also tested across the cardiac cycle. Correct localization rate did not differ significantly between systole (M = 73.27%) and diastole (M = 73.68%), $t_{36} = -0.62$, $P = 0.54$. Likewise, localization sensitivity was not significantly different between systole (M = 0.90) and diastole (M = 0.93), $t_{36} = -0.89$, $P = 0.38$ (Fig. 2*B*).

Finally, other heartbeat-associated physiological events (e.g., the pulse wave) are temporally coupled with the onset of systole. Therefore, in an exploratory analysis we assessed the effect of the absolute time delay of somatosensory stimulation from the previous R-peak on detection and localization rates. Detection and localization rates were significantly different between four time windows: 0 to 200, 200 to 400, 400 to 600, and 600 to 800 ms (within-subject ANOVA, $F_{3,108} = 7.25$, $P = 2{\cdot}10^{-4}$ and $F_{3,108} = 3.97$, $P = 0.01$). Detection and localization was lowest 200 to 400 ms after the R-peak (post hoc paired t test between 0- to 200- and 200- to 400-ms windows for detection: $t_{36} = 3.76$, $P = 6{\cdot}10^{-4}$ and localization: $t_{36} = 2.88$, $P = 0.007$; between 200 to 400 and 400 to 600 ms for detection: $t_{36} = -3.61$, $P = 9{\cdot}10^{-4}$ and localization: $t_{36} = -1.36$, $P = 0.18$; Fig. 2*C*). Significant differences were found for the sensitivity (main effect of time, $F_{3,108} = 6.26$, $P = 6{\cdot}10^{-4}$; post hoc paired t test between 0 to 200 and 200 to 400 ms, $t_{36} = 2.83$, $P = 0.008$ and between 200 to 400 and 400 to 600 ms, $t_{36} = -3.48$, $P = 0.001$) but not for the criterion ($F_{3,108} = 0.10$, $P = 0.96$; *SI Appendix*, Fig. S2).

SEPs during Diastole Compared to Systole. Conscious somatosensory perception is known to correlate with greater amplitude of certain SEP components such as N140 and P300 (20). In line with the changes in somatosensory perception, we expected to find differences in SEPs during diastole compared to systole. We systematically compared SEPs during systole and diastole in the time window of 0 (stimulation onset) to 600 ms with a cluster-based permutation t test. SEPs over the contralateral somatosensory cortex (indexed by C4 electrode) showed greater positivity when stimulation was performed during diastole than systole in two temporal clusters: 268 to 340 ms and 392 to 468 ms (Monte Carlo $P = 0.004$ and $P = 0.003$, respectively, corrected for multiple comparisons in time; Fig. 3*A*). SEPs for hits during

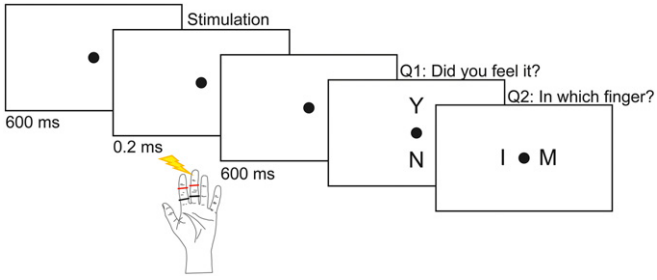

Fig. 1. Experimental paradigm. Thirty-seven subjects received a weak electrical pulse to the left index or the middle finger in 800 out of 960 trials over eight experimental blocks. Subjects were told that every trial contained a stimulus; however, in 160 pseudorandomized trials no stimulus was actually presented. In every trial, participants were asked to first perform a yes/no detection task and then a location discrimination task.

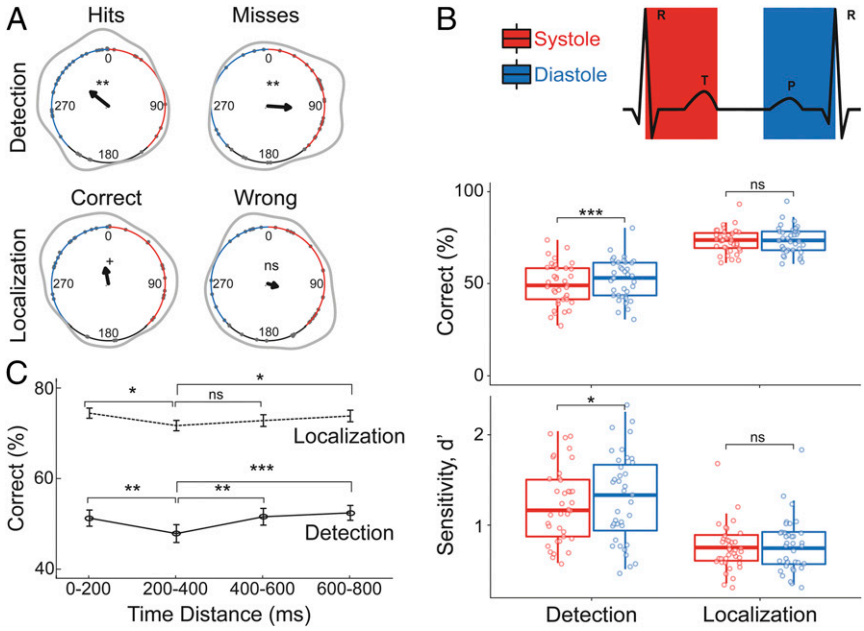

Fig. 2. Conscious detection of somatosensory stimuli varies across the cardiac cycle. (*A*) Distribution of hits (*Top Left*), misses (*Top Right*), correct localizations (*Bottom Left*), and wrong localizations (*Bottom Right*) across the cardiac cycle (the interval between two R-peaks at 0/360°). Gray points show subjects' mean degrees. The black arrows point toward the overall mean degree and its length indicates the coherence of individual means. The gray lines depict the circular density of individual means. The overall mean systole and diastole lengths are shown with red and blue, respectively. Hits and misses were nonuniformly distributed across the cardiac cycle (Rayleigh tests, $\overline{R} = 0.40$, $P = 0.003$ and $\overline{R} = 0.40$, $P = 0.004$, respectively). While correct localizations showed a trend toward a nonuniform distribution ($P = 0.067$), wrong localizations did not show a significant deviation from uniform distribution ($P = 0.35$). (*B*, *Top*) Correct detection and localization percentages during systole and diastole. Participants had more correct detections in diastole ($t_{36} = -3.95$, $P = 3{\cdot}10^{-4}$). No statistically significant difference between systole and diastole was found for correct localization ($P = 0.54$). (*B*, *Bottom*) Detection and localization sensitivity (d') between systole and diastole. Detection sensitivity was significantly higher in diastole than systole ($t_{36} = -2.38$, $P = 0.008$), and localization sensitivity did not differ significantly between the two cardiac phases ($P = 0.38$). (*C*) Correct detection and localization of somatosensory stimuli relative to their distance from the previous R-peak. Both detection and localization performances were lowest 200 to 400 ms after the R-peak. (post hoc paired *t* test between 0 and 200 and 200 and 400 ms for detection: $t_{36} = 3.76$, $P = 6{\cdot}10^{-4}$ and localization: $t_{36} = 2.88$, $P = 0.007$). Error bars represent SEMs. $^{+}P < 0.08$, $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$; ns, not significant.

diastole and systole did not differ significantly (smallest Monte Carlo $P = 0.27$). SEPs for misses, however, differed between systole and diastole over the contralateral somatosensory area. Higher positivity was observed in diastole compared to systole in time windows of 288 to 324 ms and 400 to 448 ms, respectively (Monte Carlo $P = 0.02$ and Monte Carlo $P = 0.01$, respectively; Fig. 3*C*).

We used a within-subject ANOVA with the factors detection (hit vs. miss) and cardiac phase (systole vs. diastole) to examine their effect on the P300 component of the SEPs. The P300 latency was determined in the 268- to 468-ms interval by merging the two time clusters observed for SEP differences between systole and diastole. We found significant main effects of detection ($F_{1,36} = 33.29$, $P = 1{\cdot}10^{-6}$) and cardiac phase ($F_{1,36} = 8.26$, $P = 0.007$). We did not observe a significant interaction effect ($F_{1,36} = 2.55$, $P = 0.12$).

To ascertain that the SEP differences during systole and diastole originate from somatosensory cortex, a source reconstruction was performed (see *SI Appendix*, *Methods* for details). On source level, we confirmed the significant difference in P300 amplitude during systole and diastole in the contralateral somatosensory cortex ($t_{36} = -2.55$, $P = 0.01$; *SI Appendix*, Fig. S3). In exploratory analyses, we tested SEPs in other brain areas known to influence heart–brain interactions and SEP amplitudes: right anterior insula (21), right inferior parietal lobule (rIPL; ref. 14), bilateral anterior and posterior cingulate (ACC and PCC; refs. 14 and 22) as well as bilateral lateral prefrontal cortices (LPFC; ref. 22). We did not find significant differences in the SEPs between systole and diastole in these regions (*SI Appendix*, Table S2).

HEPs Predict Somatosensory Detection. HEPs are cortical electrophysiological responses time-locked to the R-peak of the ECG and are thought to represent neural processing of cardiac activity (15, 23, 24). We tested whether HEPs immediately preceding stimulus onset predicted somatosensory detection. To ensure that the time window for the HEP, 250 to 400 ms after the R-peak (15, 23, 24), was free of neural responses to the stimulation, we only included trials where the stimulus occurred at least 400 ms after the preceding R-peak (i.e., during diastole). We averaged the EEG data locked to the R-peak separately for hits and misses and submitted the 250- to 400-ms post R-peak time window to a cluster-based permutation *t* test. Prestimulus HEPs significantly differed between hits and misses over the contralateral somatosensory and central electrodes between 296 and 400 ms (Monte Carlo $P = 0.004$ corrected for multiple comparisons in space and time; Fig. 4 *A* and *B*) with a significantly higher positivity for misses. No significant changes were found in either heart rate or HRV between hits and misses included in the HEP analyses ($t_{36} = 1.51$, $P = 0.14$ and $t_{36} = -0.61$, $P = 0.55$, respectively). Therefore, the observed differences in HEPs cannot be attributed to changes in heart rate or HRV between hits and misses (14).

Subsequently, we calculated the prestimulus HEPs averaged across the cluster electrodes in the 296- to 400-ms time window separately for different detection responses (e.g., hits and misses). Similarly, we computed HEPs for cardiac cycles outside the

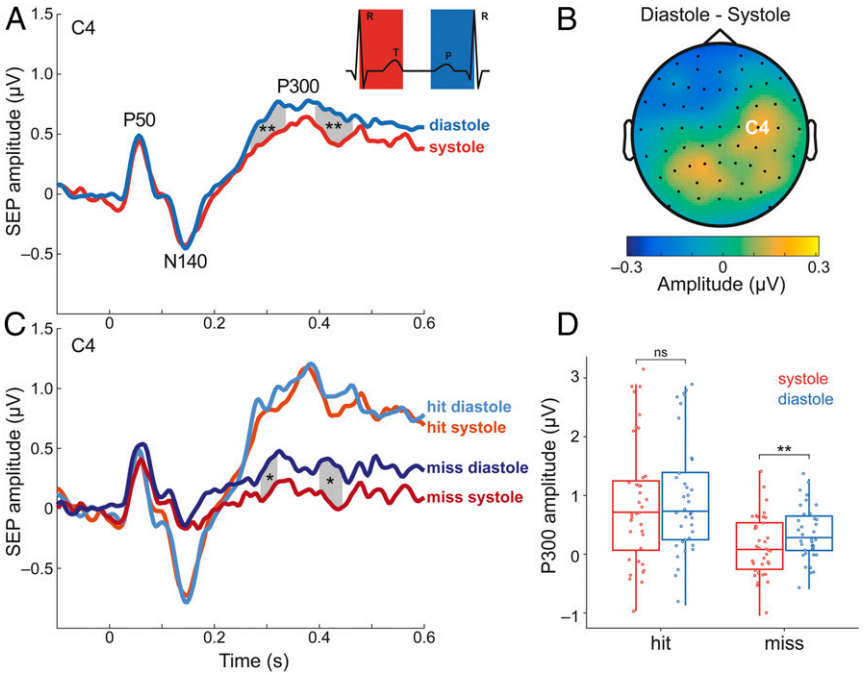

Fig. 3. SEPs for stimulations during systole vs. diastole (*A*) The difference in P300 component of SEPs (electrode C4) between systole and diastole. SEPs were more positive for stimuli during diastole than systole between 268 to 340 ms and 392 to 468 ms after stimulus onset over contralateral somatosensory cortex (Monte Carlo $P = 0.004$ and $P = 0.003$, respectively, corrected for multiple comparisons in time). (*B*) The topography contrast between diastole and systole between 268 and 468 ms. The position of electrode C4 is shown on the head model. (*C*) SEPs for hits (lighter colors) and misses (darker colors) during systole (red) and diastole (blue). SEPs showed higher positivity for misses during diastole than during systole in two time windows: 288 to 324 ms and 400 to 448 ms ($P = 0.02$ and $P = 0.01$, respectively). (*D*) The mean SEP amplitude between 268 to 468 ms for detection and cardiac phases. $*P < 0.05$, $**P < 0.005$; ns, not significant.

stimulation window (Fig. 1). Nonstimulation-related HEPs showed significantly more positivity than those preceding hits (paired *t* test, $t_{36} = 4.83$, $P = 3{\cdot}10^{-5}$) and a trend toward more positivity compared to those preceding misses (paired *t* test, $t_{36} = 1.90$, $P = 0.07$). HEP amplitudes preceding correct rejections showed significantly less positivity than HEPs preceding hits (paired *t* test, $t_{36} = 4.22$, $P = 2{\cdot}10^{-4}$) and were not significantly different from HEPs preceding misses (paired *t* test, $t_{36} = 1.63$, $P = 0.11$).

Next, we tested whether the HEP amplitude difference between hits and misses reflected a change in sensitivity or criterion according to SDT (Fig. 4 *D* and *E*). We sorted single trials according to mean HEP amplitude (across the cluster electrodes in the 296- to 400-ms time window) and split them into three equal bins (the number of HEP bins was chosen for comparability with a previous study; ref. 12) for each participant. We found that detection rates decreased as the HEP amplitude increased. Since we already showed this effect in the cluster statistics, we did not apply any statistical test here to avoid "double dipping" (25). The decrease in detection rate with increasing HEP amplitude was associated with an increase in criterion. More specifically, participants were more conservative in their decision and reported detecting the stimulus less often, regardless of their actual presence, when HEP amplitude was higher (within-subject ANOVA, $F_{2,36} = 10.30$, $P = 1{\cdot}10^{-4}$). Simultaneously, their sensitivity did not change significantly ($F_{2,72} = 0.17$, $P = 0.84$). We then tested whether prestimulus HEP amplitude could also affect somatosensory localization. Increasing HEP levels were associated with decreases in localization rate ($F_{1.72,62.01} = 10.27$, $P = 0.03$; Fig. 4*F*). Correct localization of hits and misses did not significantly differ between HEP bins ($F_{2,72} = 1.26$, $P = 0.29$ and $F_{2,72} = 0.28$, $P = 0.76$; *SI Appendix*, Fig. S4), indicating that the change in localization rate, associated with HEP amplitude, was connected with the change in detection rate.

We also tested whether prestimulus HEP amplitudes were associated with changes in SEP amplitudes. We applied a cluster-based permutation *t* test in the time window of 0 to 600 ms (0 = stimulation onset) to compare SEPs following low and high HEP amplitudes. Between 32 ms and 600 ms SEPs over the contralateral somatosensory cortex had higher positivity when stimulation was preceded by low HEP compared to high HEP amplitudes (Monte Carlo $P = 0.004$ corrected for multiple comparisons in time; Fig. 4*G*). On the source level, we confirmed that the amplitude of the earliest SEP component (P50) was significantly different following low and high HEP amplitudes in the contralateral primary somatosensory cortex (*SI Appendix*, Fig. S5). In further exploratory analyses, we tested whether differences in the P50 component could be observed in other brain areas involved in heart–brain interactions (cf. the previous section). Following high and low HEP amplitudes, there was a significant difference of P50 amplitude (false discovery rate-corrected) in the right anterior insula ($t_{36} = 3.23$, $P = 3{\cdot}10^{-3}$), the left and right PCC ($t_{36} = -4.55$, $P = 6{\cdot}10^{-5}$ and $t_{36}=-3.39$, $P = 2{\cdot}10^{-3}$), and the left and right LPFC ($t_{36} = -3.80$, $P = 5{\cdot}10^{-4}$ and $t_{36} = -4.14$, $P = 2{\cdot}10^{-4}$) but not in the rIPL and the bilateral ACC (*SI Appendix*, Table S3).

Prestimulus Sensorimotor Alpha Rhythm Predicts Somatosensory Detection and Localization. Given that alpha rhythm is known to influence sensory processing (2, 26–29), we assessed its effect on perception in our study as well as its possible interaction with heartbeat-related effects. Therefore, we sorted and divided trials into five equal bins (the number of alpha bins were chosen to be consistent with previous studies; refs. 25 and 26), according to the mean sensorimotor alpha amplitude between 300 and 0 ms before stimulus onset. We then calculated the percentage of correct detection and localization responses for every bin.

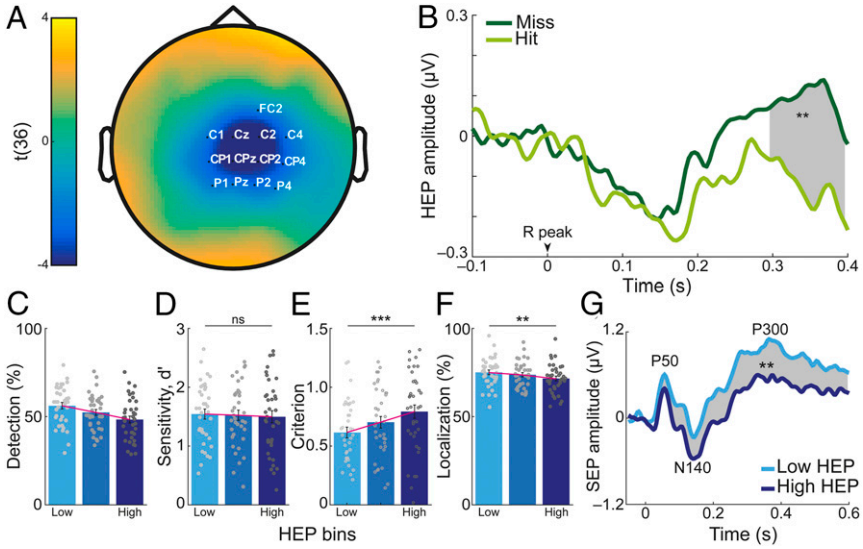

Fig. 4. HEPs before stimulus onset predicted somatosensory detection. (*A*) Topographical map of *t* values for HEP differences preceding hits and misses: Grand average across 37 participants in the 296- to 400-ms time window, where a significant difference (misses > hits) was observed on the highlighted electrodes (Monte Carlo $P = 0.004$ corrected for multiple comparisons in time and space). (*B*) Prestimulus HEPs averaged across the cluster. (*C–F*) Single-trials were sorted according to the mean HEP amplitude (across the cluster in the 296- to 400-ms time window) and split into three equal bins for each subject. (*C*) As the HEP amplitude increased, the detection rate decreased. (*D*) This decrease was not associated with a significant change in detection sensitivity ($P = 0.84$), (*E*) but correlated with an increase in criterion, that is, reporting stimulus presence less often regardless of actual stimulus presence ($P < 0.0005$). (*F*) Similar to the decrease in detection rate, correct localization rate decreased with increasing HEP amplitude ($P = 0.003$). The gray points on the bar plots represent individual subjects. (*G*) SEP amplitudes for trials in the low and high HEP bins. A significant difference in SEP amplitudes for the low and high HEP bin was observed between 32 and 600 ms poststimulation at contralateral somatosensory cortex (C4 electrode; Monte Carlo $P = 0.004$ corrected for multiple comparisons in time). Error bars represent SEMs. $^{**}P < 0.005$, $^{***}P < 0.0005$; ns, not significant.

Correct detection and localization responses decreased with increasing levels of alpha amplitude (within-subject ANOVA, $F_{2.77,99.74} = 8.88$, $P = 3{\cdot}10^{-7}$ and $F_{3.30,118.81} = 6.11$, $P = 4{\cdot}10^{-5}$; Fig. 5*B*). With increasing prestimulus alpha amplitude, participants had a more conservative criterion ($F_{4,144} = 3.77$, $P = 0.006$; Fig. 5*C*). Sensitivity did not change significantly but showed a trend toward a decrease ($F_{4,14} = 2.20$, $P = 0.07$; Fig. 5*C*).

Sensorimotor Alpha Does Not Mediate Cardiac Phase Effect on Detection. Since prestimulus sensorimotor alpha amplitude modulated somatosensory perception, we hypothesized that alpha oscillations mediated the effect of cardiac phase on detection. To test this hypothesis, we calculated detection rates separately for systole and diastole trials within each alpha bin, where alpha amplitudes were comparable ($F_{1,36} = 0.89$, $P = 0.35$). Both cardiac phase and alpha levels significantly correlated with detection rate (within-subject ANOVA test, $F_{1,36} = 15.82$, $P = 3{\cdot}10^{-4}$ and $F_{2.93,105.30} = 12.05$, $P = 1{\cdot}10^{-6}$) but there was no significant interaction effect ($F_{4,144} = 0.34$, $P = 0.85$; Fig. 5*D*). This result indicated that detection rates differed between systole and diastole in the presence of comparable sensorimotor alpha amplitude levels. Further confirmation of this relationship by fitting general linear mixed-effects models (GLMM) at a single-trial level is shown in *SI Appendix*, *Methods* and Table S4).

Prestimulus Sensorimotor Alpha Does Not Mediate the Effect of HEP on Detection. To test whether prestimulus alpha amplitude mediated the relationship between HEP and detection, detection rates were calculated separately for low and high HEP levels within each alpha bin, where alpha amplitudes were similar between low and high HEP ($F_{1,36} = 0.14$, $P = 0.71$). A within-subject ANOVA showed significant main effects of both HEP ($F_{1,36} = 38.71$, $P = 4{\cdot}10^{-7}$) and alpha amplitude levels ($F_{4,144} = 10.37$, $P = 2{\cdot}10^{-7}$) for the detection rate with no significant interaction between them ($F_{4,144} = 0.75$, $P = 0.56$; Fig. 5*E*). This result shows that the HEP effect was additive to the effect of alpha levels on detection (see also *SI Appendix*, Table S5 for additional GLMM analyses).

Controls for Volume Conduction Effect. Moreover, we ascertained that the observed SEP differences between the two cardiac phases as well as the HEP effect on detection were not likely to be explained by differences in cardiac electrical activity, which might have caused differences in the EEG by volume conduction (14, 16, 30). First, we examined whether possible ECG artifacts were successfully eliminated during the calculation of SEP differences between systole and diastole (see *Materials and Methods* for further details and *SI Appendix*, Fig. S6 *A–C*): We tested whether the ECG waveform difference between the systole and diastole trials were canceled out after ECG artifact correction (*SI Appendix*, Fig. S6 *D–F*). The comparison between two residual ECG waveforms for systole and diastole trials revealed no significant difference (no clusters were found; *SI Appendix*, Fig. S6*F*). Thus, the observed differences in SEP amplitudes between systole and diastole cannot be attributed to differences in cardiac electrical activity. Second, we checked whether the response to heartbeats preceding hits and misses differed in the ECG data. The ECG data looked similar for hits and misses (*SI Appendix*, Fig. S7*A*). The cluster statistics on the ECG data 296 to 400 ms after the R-peak did not show any significant difference between hits and misses (no clusters were found; *SI Appendix*, Fig. S7*A*). Correcting the EEG data for the cardiac artifact using independent component analysis did not significantly change the results (*SI Appendix*, Fig. S7*B*). Therefore, HEP differences preceding hits and misses cannot be explained due to differences in cardiac electrical activity.

Discussion

We show that the timing of a somatosensory stimulus, with respect to the cardiac cycle, along with the amplitude of the

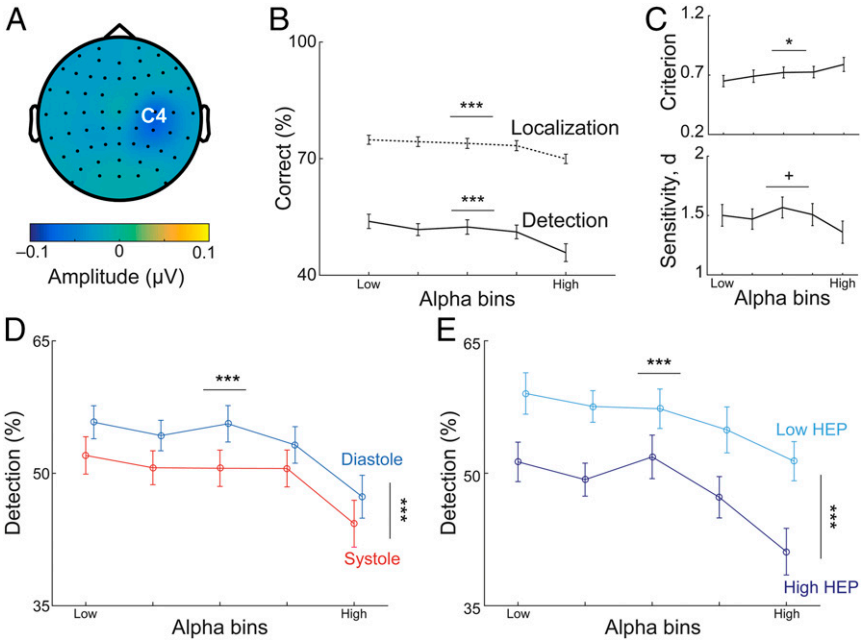

Fig. 5. Prestimulus sensorimotor alpha amplitude affects somatosensory perception but does not mediate heartbeat-related perceptual effects. (*A*) Topography of prestimulus alpha (8 to 13 Hz) difference between hits and misses in the time window of 300 to 0 ms before stimulus onset. (*B*) Trials were sorted into five equal bins of increasing mean sensorimotor alpha amplitudes in the prestimulus time window of 300 to 0 ms over contralateral somatosensory cortex (C4 electrode). Correct detection and localization rates are given for each alpha bin. Both detection and localization decreased as alpha amplitude levels increased ($P = 3{\cdot}10^{-7}$ and $P = 4{\cdot}10^{-5}$). (*C*) The decrease in detection rates with increasing alpha amplitude levels was associated with a significant increase in criterion, that is, a higher bias to miss the target ($P = 0.006$; *Top*) and a trend toward lower sensitivity ($P = 0.07$; *Bottom*). (*D*) For each alpha bin, detection rates are given separately for systole and diastole. Cardiac phase and alpha levels affected detection rate in an additive fashion (within-subject ANOVA test, $F_{1,36} = 15.82$, $P = 3{\cdot}10^{-4}$ and $F_{2.93,105.30} = 12.05$, $P = 1{\cdot}10^{-6}$). (*E*) For each alpha bin, detection rates are given separately for the trials with highest and lowest HEP, respectively. Prestimulus HEP amplitudes across the time window 296 to 400 ms after the R-peak were categorized in three equal bins for each participant, and detection rates were determined separately for the lowest and highest HEP conditions within each alpha bin. Both prestimulus factors, that is, HEP amplitudes and alpha amplitudes, influenced detection rates independently (within-subject ANOVA $F_{1,36} = 38.71$, $P = 4{\cdot}10^{-7}$ and $F_{4,144} = 10.37$, $P = 2{\cdot}10^{-7}$). Error bars represent SEMs. $^{+}P < 0.08$, $^{*}P < 0.05$, $^{***}P < 0.0005$.

prestimulus HEP shape conscious perception and the SEP. More specifically, detection rates were higher during diastole than systole and inversely related to the amplitude of the preceding HEP. Differential psychophysical effects of cardiac phase and HEP were observed on sensitivity and criterion, respectively. Furthermore, the cardiac phase influenced only late components of the SEPs (P300), whereas the effects of HEP amplitude were observed in both early (starting with P50) and late SEP components. While prestimulus alpha power also influenced perception and somatosensory processing, its effect was independent of both heartbeat-related effects on conscious perception, that is, alpha power and heartbeat-related events had an additive impact on somatosensory perception.

Our first main finding, the modulation of perception and neural response along the cardiac cycle, seems best explained by periodical modulations of perception in a predictive coding framework, in which the brain is continuously producing and updating a model of sensory input. This model not only concerns exteroceptive stimuli but also interoceptive signals such as the heartbeat. Each heartbeat and its concomitant pulse wave lead to transient physiological changes in the entire body. These repeating cardiac fluctuations are treated as predictable events and attenuated by the brain to minimize the likelihood of mistaking these self-generated signals as external stimuli (31, 32).

Of relevance for our study, heartbeat-related pressure fluctuations are tightly coupled with the firing pattern of afferent neurons in the fingers (33). These neurons fire in response to the pressure wave that reaches its maximum after around 200 to 400 ms after the R-peak within systole (34). We postulate that the same top-down mechanism, which suppresses the perception of heartbeat-related firing changes in afferent finger neurons (33), also interferes with the perception of weak external stimuli to the fingers. This would only occur if presented during the same time period in systole—and more precisely between 200 and 400 ms after the R-peak. So, we propose that there is a prediction regarding heartbeat-/pulse wave-associated neural events which leads to the suppression of weak external somatosensory stimuli occurring in this time window. This effect reflected changes in sensitivity, that is, a weak input during systole is more likely to be regarded as pulse-associated "internal noise," and thus the differentiation between the stimulation and "noise" becomes more difficult. This could also explain why localization becomes worse during systole. Interestingly, a recent modeling study suggested that predictive mechanisms leading to attenuated integration of weak and neutral exteroceptive input might give rise to higher uncertainty about environmental "risks," which the organism would compensate for by increasing the expectation for detecting fear/threat in the environment (35). This may explain why the detection of fear/threat stimuli—in contrast to our neutral somatosensory stimuli—is enhanced during systole (36).

Furthermore, we show that perceptual suppression during systole was stronger in individuals who had less HRV. Whether this latter effect is related to a possibly more accurate (temporal) prediction of the next heartbeat or another physiological mechanism associated with HRV such as the vagal tone cannot be differentiated based on our data.

A reduction of the P300 amplitude accompanied the cardiac phase-associated modulation in somatosensory perception and sensitivity during systole compared to diastole. If a peripheral mechanism (e.g., less sensitivity of receptors of peripheral nerves) were to underlie the cardiac cycle effects on perception, it would yield already a difference in earlier SEP components. Interestingly, the P300 component has been regarded as an indicator of the "prediction error" (37) such that its amplitude is expected to reduce with a more precise prediction (via a smaller prediction error). Thus, the suppression of the P300 component during systole suggests that the pulse-synchronous peripheral neural activity (33) elicits a central prediction of this peripheral neural activity. The P300 component has been also suggested to be an indicator of conscious awareness (38, 39). Fittingly, the suppression of recurrent activity within the somatosensory network in the later stages of stimulus processing would be expected to reduce P300 amplitude (38–40). Taken together, the decreased P300 amplitude and lower sensitivity for somatosensory stimuli during systole might indicate a less efficient propagation of neuronal activity to higher processing levels (41). In the context of the global neural workspace theory (38), decreased sensitivity prevents "ignition" of conscious perception of a stimulus by interfering with its processing within the higher-order sensory cortices. This prevents the broadcasting of the stimulus and therefore conscious perception of it.

Our second main finding links HEP amplitudes to the processing of weak somatosensory stimuli. Specifically, we show that HEP in the time range of 296 to 400 ms showed higher positivity for misses than hits over centroparietal electrodes. That is, the amplitude (positivity) of HEP was inversely related to detection as well as stimulus localization. Although cardiac physiology is known to modulate HEP amplitudes (42, 43), we could not detect any changes in cardiovascular measures (heart rate and HRV) with respect to HEP. However, we cannot rule out a possible effect of cardiac physiology in HEP-related effects since we did not assess all cardiac-related measures such as cardiac output. In an SDT-based analysis, we have shown that the HEP effect was mainly related to changes in the criterion, in other words, with increasing HEP, participants adopted a more conservative bias for detection. A conservative bias has been shown to be associated with lower baseline firing rate across different brain regions, pushing neurons away from the threshold for "ignition" (41). Supporting this mechanism of criterion, that is, changing baseline firing rates in the brain, we found that the increasing prestimulus HEP amplitudes had a negative effect on the amplitude of both early (P50) and later SEP components (N140, P300). In other words, we interpret the changes in SEP amplitudes as reflecting changes in criterion.

Following different levels of HEP, the source-localized P50 amplitude was also different in contralateral somatosensory cortex, right insular cortex, LPFC, and PCC. Right anterior insula has been proposed as an integral hub to mediate internally and externally oriented attention (21) that can trigger attentional switches via its reciprocal connections with the lateral prefrontal cortex—an important region for attentional control similar to PCC (44). Similar modulation of early SEP components (P50) has previously been shown along with shifts of spatial attention (27, 45). Given that HEP amplitude has been found to be significantly higher during interoceptive compared to exteroceptive attention (46–48), we propose that the modulations of HEP amplitude reflect attentional shifts between external stimuli and internal bodily states. In line with this view, it has been suggested that the sudden "ignition" of a spontaneous internal activity can block external sensory processing (49). Similarly, heartbeat-related signals, which have been suggested to contribute to spontaneously active and self-directed states of consciousness (14), might prevent "ignition" of the upcoming somatosensory stimulus. Overall, the most plausible explanation for our findings seems to be that a shift from external to internal attention, reflected by HEP amplitude increases, interferes with conscious perception of external somatosensory stimuli by decreasing the baseline firing rates within the somatosensory network. We are, however, aware that this interpretation is not definitely proven, and there might be alternative explanations, for example a modulation of overall attentional resources.

In the visual domain, a recent study also proposed that HEPs can predict the detection of weak stimuli (14). Interestingly, Park et al. (14) reported that larger heart-evoked activity measured using magnetoencephalography was associated with better external perception, while we observed the opposite pattern. These differences might be due to the different sensory modalities tested, that is, the allocation of attentional resources to interoception may vary for the detection of somatosensory and visual stimuli. In this context, it is important to note that interoception—in addition to neurotransmission via viscerosensory afferents—might be partly mediated or accompanied by somatic neurotransmission. For example, somatosensory afferents from the skin have been shown to be involved in cardiac interoception (50). Another interoceptive process, most likely to be informed by changes in the skin, is breathing. A recent study showed that when attention was directed to breathing, the somatosensory cortex showed a higher, and the visual cortex a lower, coupling to the anterior insular cortex, a key area for interoception (51). This result implies that interoception might interact with visual and somatosensory cortices differently. Furthermore, the somatosensory cortex has been indicated as one of the sources of HEPs (15, 52) and as playing a substantial role for interoception (21, 50). Therefore, it seems plausible that heart-related processes in the interoceptive cortices, notably involving somatosensory but less so visual areas, may interfere differently with the processing of exteroceptive somatosensory and visual signals.

Our third main finding relates heartbeat-associated effects to ongoing neural activity. First, we attempted to confirm the influence of prestimulus sensorimotor alpha activity on somatosensory perception as shown in previous studies (28, 53, 54). We observed that during periods of weak prestimulus alpha amplitude detection rates increased, which reflected a more liberal detection criterion. This finding is consistent with studies in the visual (26) and somatosensory domain (54). Even though detection has already been associated with lower alpha levels (2, 28, 53), the relationship between somatosensory localization and alpha amplitudes—to the best of our knowledge—has not been reported so far. In the visual domain, when localization and detection tasks were tested with a block design, detection but not localization was shown to vary across alpha levels (26). For the somatosensory domain, we showed that not only detection rates but also localization rates increased with decreasing prestimulus alpha amplitudes. Given the effect of alpha on somatosensory perception, we tested whether sensorimotor alpha oscillations modulated the heartbeat-related effects on detection. Our analysis showed that neither of the two heartbeat-related effects on perception (i.e., the cardiac phase and the HEP amplitude) was mediated by prestimulus alpha amplitude, but rather both are independent and additive to the effect of prestimulus sensorimotor alpha amplitude.

Several pathways relating cardiac activity to the brain have been suggested. Most notably, baroreceptor activation might inform cortical regions about timing and strength of each heartbeat (55). Baroreceptors are maximally activated during systole and their stimulation has been suggested to reduce cortical excitability (56). Thus, the systolic activation of baroreceptors might inform predictive mechanisms in the brain concerning when to attenuate the processing of heartbeat-coupled signals. Other than through baroreceptors, cardiac signals might also reach the cortex through direct projections of cardiac afferent neurons to the brain (57) or via somatosensory afferents on the

skin (50) as discussed above. While presently it is not clear which of these pathways is most relevant for heart–brain interactions, our results are consistent with the notion of the somatosensory cortex as an important relay center for cardiac input (15, 21, 50, 52). How this relay center modulates the relationship between interoception and exteroception is an interesting topic for future research.

In conclusion, timing of stimulation along the cardiac cycle and spontaneous fluctuations of HEP amplitudes modulate access of weak somatosensory stimuli to consciousness and induce differential effects on SEPs. We explain these fundamental heart–brain interactions within the framework of interoceptive predictive coding (stimulus timing) and spontaneous shifts between interoception and exteroception (HEP amplitudes). These findings on heartbeat-related perceptual effects might serve as an example how in general body–brain interactions can shape our cognition.

Materials and Methods

Participants. Forty healthy volunteers were recruited from the database of the Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany. Three subjects were excluded from the analysis due to technical problems during the experiment. Data from 37 subjects were analyzed (20 females, age: 25.7 ± 3.9 y [mean ± SD], range: 19 to 36 y). Some experimental blocks were excluded from the data analysis due to data acquisition failures (eight blocks from five subjects), false alarm rates >40% (eight blocks from eight subjects), responding with the wrong finger in the task (four blocks from three subjects), and observation of closed eyes during the task (three blocks from one subject). After these exclusions, a total of 274 experimental blocks with 32,880 trials in 37 subjects were analyzed. The study was approved by the Ethical Committee of the University of Leipzig's Medical Faculty (no. 462-15-01062015). All subjects signed written informed consent and were paid for their participation.

Somatosensory Stimulation and Task Design. Electrical finger nerve stimulation was performed with a constant-current stimulator (DS5; Digitimer) using single square-wave pulses with a duration of 200 μs. Steel wire ring electrodes were placed on the middle (anode) and the proximal (cathode) phalanx of the index and the middle finger of the left hand, respectively.

In the experiment, participants performed a yes/no detection and a two-alternative forced-choice localization task on every trial. At the beginning of each trial, a black dot appeared on the screen for 600 ms. Participants then expected to get stimulation on either the index or the middle finger of their left hand. Six hundred milliseconds after the stimulation, participants "were asked" (via "yes/no?" on the screen) to report as quickly as possible whether they felt a stimulus on one of their fingers or not. They responded "yes" if they felt the stimulus and "no" if not by using their right index finger. Thereafter, participants were asked to answer where the stimulation has occurred. They were explicitly told "to guess" even if they reported not feeling the stimulus in the first question. If they located the stimulus on the left index finger, they were asked to use their right index finger to answer and to use their right middle finger if they located the stimulus on the left middle finger. The next trial started immediately after responding to the localization question. In total, every participant completed eight blocks. Each block contained 100 trials with electrical stimulation (50 trials for each finger) and 20 trials without any stimulation (catch trials). The duration of each block was ∼8 min. To find stimulus intensities with 50% detection probability (i.e., threshold), we applied a two-step procedure before starting the experiment. First, we roughly estimated the lowest stimulus intensity for which participants could report a sensation by applying the method of limits with ascending intensities separately for the index and the middle finger (27, 58). Second, we used a yes/no detection task (as described above) containing catch trials and six stimulus intensities around this predicted stimulus intensity (15% below, identical to, 20%, 40%, 60%, and 80% above) for each finger. The 50% threshold intensity for each finger was estimated from the participant's psychometric function (59). To control for threshold stability, stimulus intensities were readjusted after each block.

Hit, miss, false alarm (FA), and correct rejection (CR) terms were calculated for the yes/no detection task in this study. A hit was reporting the presence of a stimulus when it was present; a miss was reporting the absence of a stimulus even though it was present. For catch trials (i.e., no stimulus was presented), an FA was reporting the presence of a stimulus, while a CR was reporting its absence. The terms "correct localization" and "wrong localization" were used to describe the localization task performance. Correct localization was reporting the stimulus location correctly; wrong localization was reporting it incorrectly.

Recordings. EEG was recorded from 62 scalp positions distributed over both hemispheres according to the international 10–10 system, using a commercial EEG acquisition system (actiCap, BrainAmp; Brain Products). The midfrontal electrode (FCz) was used as the reference and an electrode placed on the sternum as the ground. Electrode impedance was kept ≤5 kΩ for all channels. EEG was recorded with a bandpass filter between 0.015 Hz and 1 kHz and digitized with a sampling rate of 2.5 kHz. An ECG electrode connected to the EEG system was placed under the participant's left breast to record the heart activity.

Data Analysis. We applied two complementary approaches—circular and binary analysis—to examine detection and localization across the cardiac cycle (60). For these analyses, we first extracted the R-peaks from the ECG data by using Kubios HRV Analysis Software 2.2 (The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland) and visually corrected for inaccurately determined R-peaks (<0.1%). From RR interval time series during the whole experiment, we calculated the SD of RR intervals (SDNN) and natural-log transformed SDNN values to calculate HRV (61, 62).

Circular Analysis. We tested detection and localization over the entire cardiac cycle, from one R-peak to the next one, by using circular statistics, which corrects for different durations of the cardiac cycle both inter- and intra-individually and accounts for its oscillatory nature (19). We calculated the relative position of the stimulus onset within the cardiac cycle with the following formula:

$$[(\text{onset time–previous R-peak time})/(\text{subsequent R – peak time–previous R – peak time})] \times 360,$$

which resulted in values between 0° and 360° (0 indicating the R-peak before stimulus onset). The distribution of stimulus onsets was tested individually for each participant with a Rayleigh test for uniformity. Two participants were excluded from further circular analyses due to nonuniformly distributed stimulation onsets across the cardiac cycle ($\overline{R} = 0.06$, $P = 0.04$; $\overline{R} = 0.06$, $P = 0.03$). For the rest of the participants ($n = 35$), the assumption of uniform onset distributions was fulfilled. We calculated the mean phase value at which different performances occurred (detection task: hit and miss; localization task: correct localization and wrong localization) for each participant. At the group level, it was tested whether the distribution of a specific performance score (e.g., hits) deviated from the uniform distribution with Rayleigh tests (19). The Rayleigh test depends on the mean vector length out of a sample of circular data points and calculates the mean concentration of these phase values around the circle. A statistically significant Rayleigh test result indicates the nonuniform distribution of data around the circle, that is, the cardiac cycle.

Binary Analysis. Considering the biphasic nature of cardiac activity, detection and localization performances were compared between the systolic and diastolic phases of the cardiac cycle. We defined systole as the time between the R-peak and the end of the t-wave (10). We used the systolic length of each cardiac cycle to define diastole as a diastolic window of equal length placed at the end of the cardiac cycle. The equal length of systole and diastole was used to equate the probability of having a stimulus onset in the two phases of the cardiac cycle. To determine the end of t-wave, a trapezoidal area algorithm was applied in each trial (63). This method has advantages compared to an approach with fixed bins (e.g., defining systole as the 300-ms time window following the R-peak) because it accounts for within- and between-subject variations in the length of systole and diastole (i.e., the heart rate). The results of the automated algorithm were visually quality-controlled. Twenty-seven trials for which the algorithm failed to calculate t-wave end and produced an abnormal systole length (more than 4 SDs above or below the participant-specific mean systole) were removed from further binary analyses. Mean systole (and diastole) length obtained from these analyses was 333 ± 21 ms. Each trial was categorized depending on whether the stimulus occurred during systole or diastole. The average number of trials categorized as systole was 338 ± 51 and as diastole was 342 ± 59.

Data Preprocessing. EEG and ECG data were analyzed offline using EEGLAB (64) and FieldTrip (65) toolbox algorithms as well as custom-built scripts on a MATLAB platform (MathWorks Inc.). An antialiasing filter with a 112.5-Hz cutoff was used before down-sampling individual datasets to 250 Hz. After all blocks were concatenated, data were first high-pass-filtered with 0.5 Hz and then low-pass-filtered with 45 Hz using a fourth order of Butterworth filter. The EEG channels that had a flat line longer than 5 s or showed less than 85% correlation with its reconstructed activity from other channels were removed and interpolated using their neighboring channels. After a principal component analysis was applied, data underwent an independent component analysis (ICA) using an extended infomax algorithm to remove sources of heartbeat, ocular and muscle artifacts (66). ICA components with cardiac field artifact were determined by segmenting ICA components depending on the R-peak of the ECG electrode and visually selecting the components whose activities were matching the time course of R-peak and t-wave of the ECG. After removing artifactual ICA components, the artifact-free components were forward-projected for the subsequent analysis steps. Afterward, the data were rereferenced to the average reference.

SEP. Data were segmented from −1,000 to 2,000 ms with respect to stimulus onset separately for trials where the stimulation occurred during systole vs. diastole. After segmenting data, we performed baseline correction using 100- to 0-ms prestimulus window. Testing for the maximum positive deflection of the early SEP component P50 (40 to 60 ms) showed that the right primary somatosensory area, contralateral to the stimulated hand (67), was represented by the C4 electrode. Therefore, the statistical analysis of SEP amplitude was performed on the C4 electrode (68). To cancel out possible effects of blood circulation, we estimated the cardiac artifact in the EEG data. For this purpose, random triggers were placed over cardiac cycles outside the stimulation window (Fig. 1). Then, we classified the arbitrary triggers as systole or diastole depending on the position of the trigger in the cardiac cycle. After the classification, data were segmented around these triggers (−1,000 to 2,000 ms) and averaged separately for systole and diastole to estimate the cardiac artifact during systole and diastole for each EEG channel per subject. We baseline-corrected these signals 100 ms before the onset of the arbitrary triggers (*SI Appendix*, Fig. S7). To prevent any possible ECG-induced artifact on the SEPs, we subtracted the mean systolic and diastolic artifacts from the SEPs during systole and diastole trials, respectively (30).

HEPs. After preprocessing data as described above, we selected the cardiac cycles containing a stimulus. We only chose the trials in which the stimulus onset was at least 400 ms after the preceding R-peak (corresponding to diastole). We determined HEPs by segmenting the preprocessed EEG data from −1,000 to 2,000 ms around the R-peak separately for hits and misses as well as for correct localizations and wrong localizations. In this way, we could calculate the prestimulus HEPs, which have been reported between 250 and 400 ms after the R-peak (15, 23, 24).

Time-Frequency Analyses. We performed time-frequency analyses to investigate sensorimotor alpha activity locked to stimulus onset. For sensorimotor alpha, we selected ICA components representing sensorimotor rhythms to eliminate effects of the occipital alpha activity as described previously by our group (27, 68). One to seven components per participant (mean 3 ± 1 SD) were selected and included in the analysis of somatosensory oscillatory activity. We ensured that our selection of sensorimotor components corresponded to a source in primary somatosensory and motor areas in source level (see *SI Appendix*, Fig. S8 for details). Then, data were segmented (−1,000 to 2,000 ms) and ECG-induced artifacts for systole and diastole were calculated and subtracted from the data as described in the previous section. Morlet wavelet analysis was performed on every trial for frequencies from 5 to 40 Hz with number of cycles increasing linearly from 4 to 10. Thus, a wavelet at 10 Hz was 4.9 cycles long and had a temporal resolution of 0.10 s and a spectral resolution of 4.85 Hz. We focused on the effects of prestimulus alpha activity in our statistical analysis to test whether the perceptual effect of the cardiac cycle on detection is influenced by prestimulus oscillatory activity (−300 to 0 ms) over contralateral somatosensory area.

Analyses according to SDT. Sensitivity (d') and criterion (c, response bias) were calculated according to SDT (69): d' and c were calculated as z(HR) − z(FAR) and −[z(HR) + z(FAR)]/2, respectively, with HR corresponding to hit rate and FAR corresponding to false alarm rate. A log-linear correction was used to compensate for extreme false alarm proportions (70) since 2 of the 37 participants produced no false alarms. Localization d' prime was calculated as $\sqrt{2}$ * z(correct localization rate).

Statistical Analyses. Assessment of statistical significance for "two-condition comparisons" in EEG data were based on cluster-based permutation t tests as implemented in the FieldTrip toolbox (65, 71). In this procedure, adjacent spatiotemporal or spatiospectrotemporal points for which t values exceed a threshold are clustered (cluster threshold P value: 0.05). Then the cluster statistics are calculated by taking the sum of t values of all points within each cluster. The type I error rate was controlled by evaluating the cluster-level statistics under a randomized null distribution of the maximum cluster-level statistics. To determine the distribution of maximal cluster-level statistics obtained by chance, condition labels were randomly shuffled 1,000 times. For each of these randomizations, cluster-level statistics were computed and the largest cluster-level statistic was entered into the null distribution. Finally, the experimentally observed cluster-level statistic was compared against the null distribution. Clusters with a P value below 0.05 (two-tailed) were considered "significant." We expected to observe differences in SEPs over contralateral somatosensory cortex indexed by C4 electrode. Therefore, in the comparisons of somatosensory related activity, we only used cluster statistics to test whether two experimental conditions differed in time over contralateral somatosensory cortex. In contrast, we did not a priori define a spatial region for HEP analyses but expected to observe a HEP between 250 and 400 ms after the R-peak (15, 23, 24).

If the sphericity assumption was violated in within-subject ANOVA, Greenhouse–Geisser correction was applied. All statistical tests were two-sided.

Data and Code Availability. The consent forms signed by participants do not allow us to give free access to data but require us to check that data are shared with members of the scientific community. Therefore, we stored data and code in the Open Science Framework and will make the link available upon request to researchers.

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My curriculum vitae does not appear in the electronic version of my dissertation for reasons of data protection.

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