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Effects of non-invasive electric brain stimulation of the inferior frontal cortex on habituation of the acoustic startle response


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# Eidesstattliche Erklärung

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Wien, 2016 Maximilian Meyszner

# Contents

# Abbreviations

| | |
|---|---|
| ADHD | Attention- Deficit Hyperactivity Disorder |
| Ag/AgCL | silver Chloride |
| ANOVA | analysis of variance |
| ANCOVA | analysis of covariance |
| ASR | acoustic startle response |
| BIS | Barratt Impulsiveness Scale |
| dlPFC | dorsolateral prefrontal cortex |
| e.g. | for example |
| EMG | Electromyography |
| HSR | Habituation rate of the startle response |
| LSD | Lysergig Acid Dietylamide |
| MANOVA | Multivariate Analysis of Variance |
| MDMA | Methylenedioxy- Methamphetamine |
| NEO-FFI | NEO Five- Factor Inventory |
| PFC | prefrontal cortex |
| PNC | pontine reticular nucleus |
| PPI | prepulse inhibition |
| PTSD | Posttraumatic Stress Disorder |
| riPFC | right inferior frontal cortex |
| rTMS | repetitive transcranial magnetic stimulation |
| SST | Stop-Signal Task |
| STN | subthalamic nucleus |
| tDCS | transcranial direct current stimulation |
| UCS | unconditioned Stimulus |

## Abstract

Acoustic startle response (ASR) is a ubiquitous, cross-species reflexive response to abrupt and intense acoustic stimulation. Habituation of the acoustic startle response is a progressive decrease of response magnitude to repeated stimulation. Faster ASR habituation has been associated with higher impulsivity and behavioral disinhibition. Modulating inhibition of prepotent reactions using transcranial direct current stimulation (tDCS) is of high clinical demand and may provide novel insights in brain processes underlying impulsivity. We therefore applied 2 mA current in a double-blind repeated measures design on the right inferior frontal cortex (riPFC) of 31 healthy subjects. Changes in ASR habituation were assessed regarding experimental conditions (anodal, cathodal or sham stimulation) and the association between trait impulsivity and ASR habituation was further explored. Results showed that tDCS had no significant effect on ASR habituation and that trait impulsivity had no effect on baseline habituation.

Keywords: acoustic startle response, habituation, impulsivity, tDCS, riPFC

## Zusammenfassung

Der akustische Scheckreflex ist eine universelle, speziesübergreifende Reaktion auf abrupte und intensive akustische Reize. Die Habituation des akustischen Schreckreflexes wird als die progressive Abnahme der Reaktionsstärke mit wiederholter Stimulation definiert. Schnellere Habituation des Schreckreflexes wurde mit höherer Impulsivität und Enthemmtheit assoziiert. Die Modulierung der Inhibition vorherrschender Impulse durch transkranielle Gleichstromstimulation (tDCS) ist von großer klinischer Bedeutung und liefert womöglich neue Einsichten in die der Impulsivität zugrundeliegenden Gehirnprozesse. Daher wurden 31 gesunden Probanden 2 mA Strom über dem rechten inferioren Kortex (riPFC) appliziert. Veränderungen der Habituation des Schreckreflexes wurden im Hinblick auf die experimentellen Bedingungen (anodal, kathodal oder Scheinstimulation) untersucht. Weiterführend wurde die Assoziation zwischen der Persönlichkeitseigenschaft Impulsivität und der Baseline-Habituation analysiert. Die Ergebnisse zeigten, dass tDCS keinen Effekt auf die Habituation des Schreckreflexes bewirkt und dass Impulsivität keinen Effekt auf die Baseline-Habituation hat.



Schlüsselwörter: akustischer Schreckreflex, Habituation, Impulsivität, tDCS, riPFC

# 1. Introduction

## 1.1. Executive Functions and Impulsivity

A major challenge in biological psychology involves determining the basic biological underpinnings of individual differences in personality and temperament (LaRowe, Patrick, Curtin & Kline, 2006). Impulsivity has been defined as a trait leading to actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences (Bari & Robbins, 2013). It is a functional personality trait seen in healthy individuals but in more extreme forms excessive impulsivity is a component not only of juvenile and adult forms of attention-deficit hyperactivity disorder (ADHD) but also mania, substance misuse disorders, behavioral addictions, such as gambling, anti-social behavior, and related borderline personality disorders (Aron, 2010). Impulsive traits therefore reflect a broad range of psychiatric conditions and actions and advancements in treatment of impulsivity-related disorders are of high societal demand.

Executive functions play a crucial role in everyday self- regulatory and adaptive human behavior. According to the conceptual framework described by Miyake, Friedman, Emerson, Witzki, Howerter & Wager, (2000) executive functions can be classified into the domains of mental set shifting (“shifting”), maintenance and updating of relevant information (“updating”) and inhibition of dominant, automatic or prepotent reactions (“inhibition”). Within this framework impulsivity is regarded as a consequence of impaired executive functioning, in particular a dysfunctional inhibition of prepotent reactions (Hoffmann, Schmeichel & Baddeley, 2012). Prefrontal cortex function can be summarized as exertion of cognitive control by means of maintenance of patterns of activity in the prefrontal cortex (Miller & Cohen, 2001). There is accumulating evidence that the right inferior frontal cortex plays a central role in a top-down inhibitory process (Aron, Robbins & Poldrack, 2004, 2014). Inhibition is postulated to be a mechanism by which PFC performs its effects on subcortical and posterior-cortical regions to implement executive control (Aron, Robbins & Poldrack, 2004). The subthalamic nucleus (STN) contributes via a

striatal pathway to stop-signal response inhibition (Aron & Poldrack, 2006). Selective inhibition of prepotent responses is thus performed via basal ganglia networks in close relationship to the PFC (Aron, Robbins & Poldrack, 2004). A more global network of PFC projections provides an alternative route in excertion of cognitive control. Thereby, inhibition within neocortical (and some subcortical) regions takes an indirect, competitive form, with prefrontal regions targeting goal- inconsistent responses and pushing their neural activation below a critical threshold (Munakata, Herd, Chatham, Depue, Banich & O´Reilly, 2011).

The effects of PFC on inhibitive functions are typically assessed by task switching paradigms, enabling the experimenter to derive implications for cognitive control (Monsell, 2003). When in theory different acts of control often demand the explanation of different underlying processes, different acts of control can be modelled within the same mathematical framework (Logan, Van Zandt, Verbruggen & Wagenmakers, 2014). However, impulsive traits as measured by self-report questionnaires do not often correlate with behavioral measures of impulsivity (Bari & Robbins, 2013), and research indicates, that self- report measures and behavioral measures reflect different unrelated constructs of impulsive behavior (Reynolds, Ortengren, Richards & De Wit, 2006). Eysenck (1994) pointed out, that physiological measures refer to several different personality variables, thus, the expected shared variance with trait measures, such as questionnaire data, is marginal and interfered by many external variables, such as state-dependency. Neurobiological techniques, provide an additional set of tools for dissecting these varieties of impulsivity (Evenden, 1999) and deepen our understanding of the fundamental underlying processes of this multifactorial construct.

### 1.2. Habituation

Habituation can be defined as progressive decrease in frequency or magnitude of response to repeated stimulation that does not involve sensory fatigue, adaptation or motor fatigue (Thompson & Spencer, 1966, Groves & Thompson, 1970, Thompson, 2009, Rankin et al., 2009). Thus, habituation is considered a basic form of nonassociative learning, at least in animals with a nervous systems (Thompson, 2010) and probably the most elementary form of behavioral plasticity (Thompson & Spencer, 1966). The term nonassociative learning implies that the

decrease is solely accounted for by the unconditioned stimulus (US) and behavioral plasticity involves that the decrease of response strength can be interpreted as failure to predict any biologically important event (Koch, 1999).

Previous research derived a list of empirical characteristics of habituation, which lead to testable predictions, e.g. the within-session decline of response rate (Lloyd et. al., 2014, Rankin et al., 2009). The Dual- Process Theory of habituation states two opposing processes in the central nervous system, whose proportion elicits an incremental (sensitization) or decremental (habituation) behavioral response. The S-R pathway is the most direct route in the central nervous system from stimulus to response and the state system includes the pathways, systems and regions, which contribute to the general responsiveness of the organism. The contribution of habituation to the behavioral outcome is assumed in the S-R pathway, and sensitization in the state system (Groves & Thompson, 1970).

Clinical implications of the concept of habituation involve diverse health problems connected to decreased habituation, such as autism spectrum disorder (Cunningham & Schreibman, 2008), obesity (Epstein et al., 2008), schizotypy (Cadenhead, Geyer & Braff, 1993) and psychopathy (Anderson, Wan, Young & Stanford, 2011), or increased habituation, such as ADHD (Iaboni, Douglas & Ditto, 1997).

### 1.3. Habituation of the acoustic startle response

Research suggests that an important aspect of impulsivity may be fast habituation to external stimuli (Lloyd, Medina, Hawk, Fosco & Richards, 2014). Acoustic startle response (ASR) is a ubiquitous, cross-species reflexive response to abrupt and intense acoustic stimulation. It involves a quick contraction of the orbicularis oculi muscle which closes the eye 30-50 ms after stimulus onset of an auditory stimulus and can be easily quantified using electromyography (EMG). ASR has been broadly used to study the neuronal, emotional, and cognitive basis of brain information processing (Blumenthal, Cuthbert, Filion, Hackley, Lipp & van Boxtel 2005). One of the fundamental features of ASR is habituation, i.e., a decrease in ASR with repeated stimulation. LaRowe, Patrick, Curtin & Kline (2006) reported that faster ASR habituation was associated with higher impulsivity and behavioral disinhibition.

ASR is mediated by the caudal pontine reticular nucleus (PNC), a neuronal circuit located in the lower brainstem (Koch, 1999). Giant neurons in the PNC receive input from cochlear, trigeminal and vestibular nuclei and project directly to motoneurons. PNC neurons integrate modulatory input from different brain regions by either enhancing or inhibiting startle response in this primary ASR pathway (Bosch & Schmid, 2006).

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### 1.4. ASR as a biomarker

There are substantial links between individual differences in personality and the habituation processes in ASR. Differences in habituation rate can be described in terms of biological markers for personality differences (Blanch, Balada & Aluja 2014). A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention (Biomarkers Definition Working Group, 2001). The application of biomarkers is discussed in the assessment of psychiatric conditions, such as diagnostics, prediction of the natural outcome of the condition and evaluating particular treatments as well as the assessment and prediction of personality or behavioral traits. For this reason biomarkers provide a promising component for individually tailored diagnostics and treatment (Singh & Rose, 2009). ASR habituation is a stable neurobiological measure and thus can be considered as a potential biomarker for both the study of individual differences and clinical diagnostics. Changes in normal inhibition and habituation of the startle response may provide trait markers for illnesses such as schizophrenia (Cadenhead, Carasso, Swerdlow, Geyer & Braff, 1999). Given the well- established finding, that PFC functions include inhibition of actions, measures of impulsivity may serve as neurobehavioral biomarkers for substance use disorders (Volkov, Koob & Baler, 2015). Marin et al. (2010) suggest the existence of a common base between impulsivity and startle habituation as vulnerability markers for alcohol dependence. Zoladz & Diamond (2013) report that exaggerated startle response may be a pre-existing risk factor for PTSD as well as an outcome of trauma. Concerning diagnostics and treatment of ADHD, Wallis (2010) points out, that stable biomarkers would eliminate the subjective diagnoses based on interviews and potentially allow for earlier diagnosis and personalized medicine. Shin et al. (2011) report, that the

reduction of startle response preceded by a weaker stimulus (prepulse inhibition, PPI) is deficient in schizophrenia patients and unaffected relatives, suggesting that it may be a trait marker for individuals at risk for developing the disorder. Combining results therefore lead to the conclusion that advances in creating impulsivity-related measures as biomarkers provide an auspicious perspective on predictive refinements and personalized treatment of various disorders.

### 1.5. Modulation of impulsivity

Transcranial direct current stimulation (tDCS) is a non-invasive and safe method for modulating brain activity. In tDCS, a weak electrical current is delivered through electrodes attached to the scalp, resulting in changes of excitability of the underlying cortical area (Nitsche & Paulus, 2000). The polarity of the current influences excitation of the underlying cortex in a differential way, whereupon positive polarization (anodal) and negative polarization (cathodal) show opposing effects. Numerous studies have confirmed that tDCS is well-suited to manipulate cognition and brain information processing (Coffman, Clark & Parasuraman, 2014) and that tDCS can induce beneficial effects in brain disorders (Nitsche et al., 2008). Noninvasive brain modulation techniques have recently gained credit as promising tools for investigating the neural substrates of high-level cognitive functions (Stramaccia et al., 2015). Knoch et al. (2006, 2007) found out, that repetitive transcranial magnetic stimulation (rTMS) of the right inferior frontal cortex (riFC) alters decision making towards riskier decisions, concluding that the riFC plays a crucial role in inhibiting responses. Modulating the rIFC by application of tDCS also resulted in changes of impulsivity, whereby the cathodal (inhibiting) condition led to enhanced impulsivity (Beeli, Casutt, Baumgartner & Jäncke, 2008). Recently, a study found out, that participants, who received anodal tDCS showed improved cognitive impulse control (Quellett et al., 2015). Ditye, Jacobson, Walsh & Lavidor (2013) pointed out, that tDCS- combined cognitive training is an effective tool for improving the ability to inhibit responses. Lesion studies suggest, that the riFC is functionally closer related to response inhibition than the dlPFC (Aron & Poldrack, 2004. 2014). Nevertheless, dlPFC, is consistently linked to response inhibition.

Fecteau et al. (2007) reported, that bilateral (left cathodal/right anodal) stimulation of the dorsolateral prefrontal cortex (dlPFC) decreased risk taking in a

Balloon Analogue Risk Task. In a further study (Fecteau et al. 2007b) anodal tDCS over dlPFC by itself did not significantly change risk-taking behaviors; however, when the contralateral dlPFC was modulated with cathodal tCDS, a decrease in risk- taking was observed. Beeli et al. (2008) found out, that measures reflecting impulsiveness, such as the Go- Nogo-Task were modulated by application of cathodal tDCS to the right dlPFC and that excitation of the dlPFC (by applying anodal tDCS) leads to a more careful driving style in virtual scenarios (Beeli at al., 2008b). Concerning clinical applications of tDCS in impulsivity-related dysfunctions, Fregni et al. (2008) showed, that craving for food was reduced by anode left/cathode right tDCS of the dlPFC. Alcohol craving (Boggio et al., 2008) and smoking craving (Fregni et al. 2008b) following a similar decreasing pattern.

When using tDCS over the dlPFC with a specific set of parameters it is possible to modulate a specific cognitive function, but a given stimulation protocol may modulate various other cognitive functions in similar or opposite directions. Despite numerous noninvasive brain modulation studies, the effects of tDCS on PFC functions such as inhibition therefore remain unclear. Most of the tDCS-studies of the PFC suggest a larger effect in anodal stimulation conditions (Tremblay, Lepage, Latulipe-Loiselle, Pascual-Leone & Théoret, 2014).

To summarize these findings: Within the framework of executive functions impulsivity can be regarded as impairment of inhibiting prepotent responses. ASR habituation is associated with higher impulsivity and behavioral disinhibition and is considered a potential biomarker for the study of individual differences. tDCS of dlFC and the riFC is linked to effects altering impulsive behavior, but it remains unclear, whether specific functions can be modulated by tDCS accordant to directional hypotheses.

### 1.6. Objective and hypothesis

The aim of this study is to assess the effects of tDCS of rIFC on habituation of ASR, a marker of behavioral inhibition. We hypothesize that the anodal tDCS of rIFC will decrease while the cathodal tDCS will increase the rate of ASR habituation. A further goal of this study is to assess the value of the habituation of the ASR as a potential biomarker for impulsivity. We therefore examine the relationship between trait impulsivity and ASR as a physiologic measure of impulsivity. We hypothesize

that higher trait impulsivity increases ASR habituation moderately, whereas lower trait impulsivity decreases ASR habituation moderately.

# 2. Methods

## 2.1. Study Design

The present study was designed as a double-blind experiment with two experimental groups and one control group. All subjects were randomly divided into three groups. Each subject was tested twice at a baseline and following tDCS (anodal, cathodal or sham condition). The testing sessions were separated at least by four days. ASR was measured before and immediately following tDCS using the SR-HLAB (San Diego Instruments Test System). Trait impulsivity was assessed, using the stop-signal task, the Go/No Go- Task and Barratt Impulsiveness Scale (BIS-11) (Preuss et al., 2007) during the first session.

## 2.2. Participants

For this study male participants were recruited via online advertisements, flyers and the data base for participants of the Social, Cognitive and Affective (SCAN) - Unit. Responders were asked to fill out a short version of the M.I.N.I. International Neuropsychiatric Interview (Sheehan et al., 1998) for initial screening purposes. Participants were invited to the laboratory if they fulfilled the following criteria: excellent german language skills, right-handedness, no history of neurological or psychiatric illness (such as schizophrenia or depression) in the participant himself or a first-degree relative , no recent intake of psychoactive medication, and no history of drug abuse, no hearing impairment, non-smokers, no skin problems such as dermatitis or birthmarks in the head region and no metal plates in the head region. Women were not included because of hormonal fluctuations during their menstrual cycle, which influence PPI of the ASR (Swerdlow, Hartman & Auerbach, 1997). PPI was explored for another study and results are discussed elsewhere.

For their participation in both testing sessions every subject received a monetary compensation of 20 Euros. If participants did not take part in both testing

sessions, they received 10 Euros for the participation in the first testing session. Since participant acquisition proved difficult the monetary incentive was set higher (40 Euros for both testing sessions, respective 20 Euros for one testing session). Results did not differ systematically across these potentially different conditions.

Cigarette, alcohol and coffee intake was interdicted for participants 24 hours prior to the testing sessions (Braff, Geyer & Swerdlow, 2001) to minimize the effects on startle magnitude and habituation. Participants who showed clear startle response in the first testing session and met inclusion criteria were invited to participate in the second testing session. In addition, they were advised to be well rested and not to wear contact lenses on both sessions, or hair gel on the second session. Prior to the measurements the study procedure was fully explained by the experimenters and all study participants provided written informed consent.

Thirty one subjects of the initial 66 testing subjects participated in both testing sessions (46,9 %). Subjects were between 19 and 37 years old (mean age= 26,03 ± 5,17 [SD] years). One outlier was detected whose baseline habituation mean during the last block deviated from the rest of the sample, but since the case had no effect on the outcome of the analysis, was kept in the sample. Five subjects were pretested in February 2015 in order to adjust the experimental procedure. Results of the pretesting sessions were not included to the main data analysis. The main data collection was carried out from March to July 2015.

### 2.3. Procedure

Both testing sessions were carried out in the laboratory of the SCAN-Unit at the University of Vienna. The procedure was in agreement with the Declaration of Helsinki and was approved by the Ethical Committee of the University of Vienna. The study was financially supported by the Slovak Academy of Sciences.

#### 2.3.1. Initial test session

After arrival at the laboratory participants were asked to read the informed consent carefully and ask questions if necessary. If participants signed the informed consent the experimenters addressed unclear or contradictory results in the screening version of M.I.N.I. International Neuropsychiatric Interview (Sheeran et al., 1998). More detailed anamnestic questions were asked to exclude participants with a mental

or neurological disorder. Then, urine samples of the participants were collected and tested for cotinine, cannabis, amphetamines, methamphetamine, MDMA, cocaine, barbiturates, benzodiazepines, LSD, and opiate use. Participants were excluded on the basis of any positive urine test result.

Following the initial anamnesis participants underwent a structured interview concerning their consumption of psychoactive substances such as nicotine, coffee, alcohol, cocaine, MDMA (ecstasy), cannabinoids, methamphetamines, opiates, hallucinogens, ketamine and organic solvents. For each substance participants reported the most recent date of consumption, frequency and past use. The structured interview was performed beside the urine tests to investigate behavioral tendencies towards drug use in a longer time frame than urine tests typically cover. Then, a buccal smear sample was taken for genetic analysis. To further exclude participants with hearing impairments white noise sounds were presented in decreasing intensities (55, 45, 35 and 25 dB) via audiometric insert headphones and subjects confirmed perception of the threshold sound with a hand signal. One participant was excluded because of hearing problems. If participants fulfilled the criteria, the baseline test session was initiated. Baseline ASR and PPI was recorded (see following section) and after completion participants worked on the Go No Go- Task and the SST in randomized order.

Then, the questionnaire battery, consisting of the Edinburgh Handedness Inventory (Oldfield, 1971), the Barratt Impulsiveness Scale (Preuss et al., 2008), NEO-FFI (Borkenau & Ostendorf, 1993), the Schizotypal Personality Questionnaire (SPQ) (Klein, Andresen & Jahn, 1997), and the Adult ADHD Self- Report Scale (WHO, 2012), was worked on by the participants. The Schizotypal Personality Questionnaire (SPQ) (Raine, 1991; Klein, Andresen & Jahn, 1997) was administered to further exclude participants because of deviating habituation to orienting stimuli and deficits, regarding executive functioning found in patients with Schizotypal Personality Disorder (Raine, 1997, Moritz et al., 1999). None of the remaining 31 participants showed deviations in the subscales assessed by the SPQ and all means were ± 1 SD below the reported means by Raine (1991, 1993), or more recently Wuthrich & Bates (2005). The Adult ADHD Self-Report Scale (WHO, 2012), a screening instrument, was assessed to exclude participants, who show core symptoms of ADHD. None of the remaining 31 participants was excluded on the basis of self- reported ADHD symptoms. Total length of the initial test session varied between 1,5 and 2 hours.

### 2.3.2. Main test session and tDCS

Upon arrival in the laboratory the experimenters checked if participants got enough sleep, did not to use hair gel, abstained from alcohol 24 hours before the main testing session, and abstained from coffee at least two hours before the test session. Then, a urine probe was inspected for drug use since the last test session. If the test result was negative, a practicing version of the SST was conducted by the participants, because of the higher degree of difficulty compared to the Go/No Go-Task.

After completion of preparations of EMG recordings (see earlier section) tDCS was prepared. Rubber stimulation electrodes were used. The active electrode (3x3 cm) was placed between position F8 and F4 (Koessler et al., 2009, Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015) and the reference electrode (5x7 cm) was placed over left supraorbital area. Electrodes were fixed using Ten20 conductive gel (Biopac Systems, Inc.), a rubber band and a bathing cap.

For anodal and cathodal tDCS 2 mA current was applied for 20 min via rubber stimulation electrodes. Sham stimulation simulated real tDCS by fixing the electrodes the same way, but no current was applied. Auditory stimulation was started 8 minutes after tDCS began. After tDCS and auditory stimulation was applied, participants worked on the SST and Go/No Go-Task. Main test session lasted approximately between 1 and 1,5 hours.

## 2.4. Auditory Stimulation

Acoustic stimuli (intensity = 105 dB, duration = 40 ms, number of stimuli, session 1 = 69, number of stimuli, session 2= 37, intertrial interval = 10-20 s) was delivered via audiometric insert headphones (Etymotic ER-2) in both sessions. Background white noise (55 dB) was presented continuously. Total auditory stimulation lasted 25 min in the initial test session and 12 min in the main test session. Acoustic stimuli were presented in 3 blocks. The first block consisted of 5 pulse-alone trials (104 dB, 40 ms). The second block consisted of 10 pulse-alone trials and 60 prepulse- (75dB, 20 ms) pulse trials. The prepulse-pulse trials

differentiated by the amount of passed time between the prepulse and the pulse. 5 different epochs were examined (30 ms, 60 ms, 120 ms, 2000 ms and 4000 ms), each consisting of 10 trials. Block 3 consisted of 4 pulse-alone trials. Auditory stimulation of the initial test session totaled 69 trials. Auditory stimulation in the main test session consisted of 37 trials total. The first block contained 4 pulse-alone trials, the second block included 30 trials, 5 times each epoch (30 ms, 60 ms, 120 ms, 2000 ms and 4000 ms) and the third block consisted of 3 pulse-alone trials.

### 2.6. EMG Recording

Participants were instructed to turn out their phone and remove all metal objects during EMG recording. Following Blumenthal et al. (2005) two Ag/AgCl ring electrodes were placed on the skin surface above the orbicularis oculi muscle. Skin was prepared with a needle and rubbing the skin with a pad to maximize impedance. Recording electrodes were attached below the lower eyelid in line with the pupil in forward gaze and 2 cm lateral to the first electrode. The ground electrode was placed at the mastoid. Participants were asked to blink in order to examine the contraction of the orbicularis oculi muscle and potentially adjust electrode placement. Electrodes were fixed with double- sided adhesive collars and electrode adaptors were filled with high conductive electrode gel. Electrode impedances were checked and the skin was abraded with a needle and electrode adaptors were filled with electrode gel again if they exceeded 3 kΩ. Participants sat approximately 10-15 cm in front of a folding screen and were instructed to avoid any movements, muscular tension, to look straight through the folding screen, keep their eyes open and avoid unnecessary blinking.

### 2.8. EMG processing and analysis

EMG data was processed using the MATLAB-based software toolbox EEGLAB (Delorme & Makeig, 2004) before data analysis. EMG was digitally filtered in the range 28-800 Hz and a 48-52 Hz notch filter was used to eliminate 50 Hz

interference. Epochs from -100 to 400 ms with respect to startle stimulus onset were selected, visually inspected and trials containing artifacts were removed. Startle response was detected as the maximum EMG voltage in the time interval 20–150 ms following stimulus onset. Mean blink amplitudes were calculated for each subject, session (treatment) and condition (anodal, cathodal or sham condition).

The following startle response measure was examined:

(I) The mean for each subjects and block was calculated. Resulting ASR amplitudes in two different pulse-alone blocks throughout the test sessions were analyzed.

(II) Habituation rate of the startle response (HSR) over the session, computed as (1- MA3/ MA1) * 100%, where MA1 and MA3 denote mean startle response within block 1 and 3 respectively.

Habituation rate was calculated as a startle response measure by subtraction of the mean baseline habituation from mean treatment habituation in order to account for changes in mean habituation amplitude by the experimental condition.

## 2.9. Statistical Analysis

All analyses were carried out using Statistical Package for the Social Sciences (SPSS, version 23.0) with an α-level for statistical significance set at 0.05 unless otherwise stated. Outliers were detected using boxplots, histograms and descriptive statistics. Values lower/higher than the 25th/75th percentile minus/plus 1.5 times the interquartile range of the group were considered outliers. Separate analyses have been run in order to detect the effect of outliers on the analysis. A two-way within subjects ANOVA with factors session (baseline, stimulation) and block (initial, final) was computed in order to examine habituation effects in both test sessions. A one-way ANOVA was run to test the effects of the different stimulation conditions on ASR

habituation. As an alternative to the one-way ANOVA, the influence of the different experimental conditions on ASR habituation was investigated by a mixed design ANOVA with within-subjects factors session (baseline, stimulation) and block (initial, final) and between-subjects factor stimulation (anodal, cathodal, sham). To examine possible covariates, Pearson correlation was calculated between baseline habituation and NEO-FFI and BIS subscales. A mixed design ANOVA with ASR as a dependent variable, BIS group as a between subjects factor and block as a within subjects independent variable has been calculated in order to determine the effect of high vs. low BIS scorers on mean amplitudes of baseline startle habituation in the first and third block of baseline measurement.

## 3. Results

A two-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences in ASR amplitudes in two different pulse- alone blocks throughout the test sessions. There were outliers in the data, as assessed by inspection of the boxplots of the mean amplitudes of the two different blocks. Since outliers did not affect the outcome of the analysis they were kept in the analysis. Mean amplitude of the third block was not normally distributed for the baseline, as well as the treatment session, assessed by Shapiro Wilk´s test ($p < .05$). Data has therefore been log-transformed and separate analysis has been run on the log- transformed and the original data. Results in the log-transformed data did not differ from the original data. Therefore the following results refer to the original data.

There was a significant effect of block on ASR amplitude $F (1, 31) = .000$, $p < .001$, partial $\eta 2 = .688$. No significant effect of session on ASR amplitude could be identified, $F (1, 31) = .682$, $p > .05$, partial $\eta 2 = .005$. The interaction term between session and block was not significant, $F (1, 31) = .117$, $p > .05$, partial $\eta 2 = .077$. (see table 2, table 3 for comparison of log-transformed data, figure 1). Pairwise comparisons showed that there was a decrease of ASR amplitude from block 1 to block 3 of 76,063 mV, SE = 9,202 mV. 95% CI [57.296 mV, 94.830 mV], $p < .001$.

In order to examine treatment effects on habituation rate, a one-way ANOVA was computed. Treatment effects increased from anodal (n= 11, M= -22,46 mV, SD= 79,39 mV) to cathodal (n= 11, M= 11,45 mV, SD= 93,57 mV) and from anodal to sham condition (n=10, M= 12,11 mV, SD= 81,48 mV). Treatment effects did differ between cathodal to sham condition (see figure 2). One outlier was detected. Further analysis kept the outlier because it did not affect the outcome of the ANOVA. Habituation was normally distributed for the anodal condition as assessed by Shapiro-Wilk's test ($p > .05$) and visual inspection of histograms and Q-Q plots. For the cathodal and sham condition, habituation was not normally distributed ($p < .05$). However, since sample sizes for each group were nearly equal, deviations to the assumption of normality can be tolerated (Liz, Keselman & Keselman, 1996). There was homogeneity of variances, as assessed by Levene's test for equality of variances ($p = .915$). Habituation was not statistically significantly different across the different stimulation conditions $F(2, 29)= .582$, $p > .05$. The group means were not statistically significant different ($p > .05$) and, therefore, we cannot reject the null hypothesis and we cannot accept the alternative hypothesis: Mean Habituation rates were not statistically different across different stimulation conditions (see table 4).

A mixed design ANOVA with within-subjects factors session (baseline, stimulation) and block (initial, final) and between-subjects factor stimulation (anodal, cathodal, sham) was computed as an alternative to the one-way ANOVA. There was a significant effect of block on ASR amplitude $F(1, 31) = .000$. $p < .001$, partial $\eta 2 = .712$. There was no significant interaction of session and stimulation, block and stimulation or session, block and stimulation (see table 5, figure 3). Correlational results did not indicate associations between baseline habituation and BIS scores or NEO-FFI- scores (see table 6). However, a mixed design ANOVA with ASR as a dependent variable, BIS group as a between subjects factor and block as a within subjects independent variable has been calculated in order to determine the effect of high vs. low BIS scorers on mean amplitudes of baseline startle response in the first and third block of baseline measurement. BIS scores therefore have been median split. BIS scores classified high were above the median, as inspected by descriptive statistics. Startle habituation was assessed in two different blocks at the beginning and at the end of the experiment. There was a significant effect of block on ASR amplitude $F(1, 30) = .000$, $p < .001$, partial $\eta 2 = .635$. No significant effect of trait

impulsivity as measured by BIS scores could be identified. $F(1, 30) = .563$, $p > .05$, partial $\eta 2 = .011$. (see table 7).

## 4. Discussion

This study investigated the effects of tDCS on ASR habituation. Contrary to our expectations, subjects did not differ across experimental conditions regarding ASR habituation. No effect of tDCS stimulation on ASR habituation could be found. Trembley et al. (2014) recently discussed how tDCS can affect PFC function, concluding that the wide array of cognitive functions that can be modulated simultaneously makes it difficult to predict its precise outcome. The between-subjects variance of the amount of current actually given to the participants may differ considerably because the impact of tDCS is subjected to confounding processes (e.g. size and shape of participants´ head, fat tissue amount, different location of brain regions underlying specific cognitive functions). Although results did not reach significance, a descriptive trend from anodal to cathodal condition in the hypothesized way could be identified. A larger sample size would therefore be beneficial with respect to effect sizes. A possible explanation of our results can be derived from Fecteau et al. (2007a): Bilateral neuromodulation of the dlPFC can lead to behavioral changes in risk taking under ambiguity, whereas no significant behavioral change was observed with unilateral neuromodulation of the dlPFC. Again, the confounding effects are specified here in terms of lateral effects of tDCS on behavioral changes in risk taking. Therefore the confirmation of our hypotheses concerning the outcome of tDCS would possibly benefit from bilateral stimulation.
It was further shown, that habituation of the ASR did occur across conditions in a stable and predictive way, showing that our experimental manipulation worked in the hypothesized way across conditions. A decreased response rate was identified both in the initial test session and in the main test session (figure 1).

Results suggest that there is no association in baseline ASR amplitudes and total BIS scores. Trait impulsivity had no statistically significant effect on startle reactivity in both blocks of baseline testing of startle habituation. Therefore, this result proposes that physiological and self- report measures of impulsivity represent unrelated constructs of impulsive behavior. A major limitation of this approach is the

artificial dichotomization of high/low impulsivity at the sample median. MacCallum, Zhang, Preacher & Rucker (2002) argue, that there are substantial negative consequences in most circumstances in which it is used, and that in most cases loss of measurement reliability and loss of information about individual differences recommend a cautious interpretation of these results. However, our results were not significant and the question of whether trait impulsivity as measured by questionnaire data has an influence on mean amplitude of ASR habituation of the 2 baseline blocks of pulse-alone trials therefore cannot be answered exhaustively.

Lane, Franklin & Curran (2013) have discussed the limitations of means-based analysis in particular when describing startle habituation: They artificially condense ASR habituation into blocks of trials, hence information about changes that occur between trials, is lost. Secondly means-based analysis often are unable to describe specific rates of habituation or changes across trials or individuals. Third, when grouping startle reactivity into blocks differences in habituation (i.e., slope) may be confounded with differences in initial startle reactivity (i.e., intercept). In conclusion, time-dependent changes in response magnitude cannot be thoroughly accounted for by block-to-block comparisons (Petrinovich & Widaman, 1984).

The limitations of both means-based analysis of startle habituation and dichotomization of quantitative personality measures can be overcome by the LCM approach. Within the structural equation modeling (SEM) framework these models have random intercepts and random slopes that permit each case in the sample to have a different trajectory over time. The random coefficients are incorporated into SEMs by considering them as latent variables (Bollen & Curran, 2006). The LCM provides additional information about ASR habituation (e.g. rate of change throughout the trajectory) and allows us to draw authoritative conclusions about the influence of a continuous exogenous variable, such as trait impulsivity on ASR habituation (Lane et al., 2013). This remains subject to further research.

## 5. Conclusion

This study found no effects of tDCS on ASR habituation. A trend in the hypothesized direction in the anodal condition could be identified. Statistical analysis

did not show a significant effect of tDCS on ASR habituation. A manipulation check revealed that ASR habituation was manipulated by our experimental paradigm in a stable and predictive way. Further results concerning personality measures indicate that trait impulsivity had no influence on ASR habituation, but have to be taken cautiously because of methodological considerations.

## 6. Literature


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## 7. List of tables

***Table 1:**: Descriptive Statistics of Trait Variables.*

| | Mean | SD | Min | Max |
|---|---|---|---|---|
| Age | 26.03 | 5.17 | 19 | 37 |
| NEO-FFI: | | | | |
| Neuroticism | 14.71 | 5.821 | 5 | 30 |
| Extraversion | 30.06 | 5.674 | 18 | 38 |
| Agreeableness | 32.06 | 6.218 | 18 | 43 |
| Openness | 34.35 | 5.748 | 23 | 45 |
| Conscientiousness | 34.65 | 6.626 | 18 | 46 |
| | | | | |
| BIS total | 58.29 | 7.9044 | 44 | 76 |
| 2nd Order Factors: | | | | |
| Attentional Impulsivity | 15.097 | 2.7490 | 9 | 21 |
| Motor Impulsivity | 22.581 | 3.9814 | 14 | 32 |
| Nonplanning Impulsivity | 20.484 | 2,8853 | 14 | 26 |
| | | | | |
| 1st Order Factors: | | | | |
| Attention | 8.94 | 1.750 | 6 | 13 |
| Cognitive Instability | 6.06 | 1.692 | 3 | 10 |
| Motor | 22.581 | 3.9814 | 14 | 32 |
| Perseverance | 7.13 | 1.668 | 5 | 12 |
| Self- Control | 10.77 | 2.276 | 6 | 14 |
| Cognitive Complexity | 9.71 | 1,637 | 6 | 14 |
| | | | | |
| SPQ total | 9.97 | 7.102 | 0 | 34 |
| Ideas of Reference | 1.45 | 1.338 | 0 | 5 |
| Excessive Social Anxiety | .71 | .938 | 0 | 4 |
| Odd Beliefs or Magical Thinking | .39 | 1.145 | 0 | 6 |

| | | | | |
|---|---|---|---|---|
| Unusual Perceptual Experiences | .61 | 1.116 | 0 | 5 |
| Odd or eccentric behavior | 1.16 | 1.530 | 0 | 5 |
| No close friends | 1.13 | 1.432 | 0 | 5 |
| Odd speech | 2.23 | 2.093 | 0 | 8 |
| Constricted Affect | 1.26 | 1.341 | 0 | 6 |
| Suspiciousness | 1.03 | .983 | 0 | 3 |

Means, standard deviations (SD), minimal and maximal values of subject's questionnaire data and age (N= 31).

**Table 2**: Statistical Analysis of original ASR amplitudes (Two-Way Repeated Measures ANOVA).

| Source of Variance | Type III Sum of Squares | df | df2 | *Mean Square* | F | Sig. |
|---|---|---|---|---|---|---|
| Session | 184.525 | 1 | 31 | 184.525 | .171 | .682 |
| Block | 185138.776 | 1 | 31 | 185138.776 | 68.327 | .000[1] |
| Session*Block | 2014.013 | 1 | 31 | 2014.013 | 2.601 | .117 |

*Note*:

[1] $\eta^2 = .688$

**Table 3**: Statistical Analysis of log-transformed ASR amplitudes (Two-Way Repeated Measures ANOVA).

| Source of Variance | Type III Sum of Squares | df | df2 | *Mean Square* | F | Sig. |
|---|---|---|---|---|---|---|
| Session | 2,361 | 1 | 31 | 2.361 | .000 | .994 |
| Block | 7.416 | 1 | 31 | 7.416 | 94.681 | .000[1] |

*Note*:

[1] $\eta^2 = .753$

**Table 4**: Statistical Analysis of Treatment Effects (One-Way ANOVA).

| Source of Variance | Sum of Squares | df | *Mean Square* | *F* | *Sig.* |
|---|---|---|---|---|---|
| Habituation | 8462,66 | 2 | 4231,33 | .582 | .565 |
| Within Groups | 210685,98 | 29 | 7265,03 | | |
| Total | 219148,46 | 31 | | | |

**Table 5:** Statistical Analysis of Treatment Effects (Mixed Design ANOVA)

| Source of Variance | Type III Sum of Squares | df | df2 | *Mean Squares* | *F* | *Sig.* |
|---|---|---|---|---|---|---|
| Session | 182.953 | 1 | 29 | 182.953 | .166 | .686 |
| Session*Stimulation | 1588.147 | 2 | 29 | 794.073 | .722 | .494 |
| Block | 184884.772 | 1 | 29 | 184884.7 | 71.549 | .000[1] |
| Block*Stimulation | 9059.995 | 2 | 29 | 4529.998 | 1.753 | .191 |
| Session*Block | 2078.893 | 1 | 29 | 2078.893 | 2.634 | .115 |
| Session*Block*Stimulation | 1122.292 | 2 | 29 | 561.146 | .711 | .499 |

Note:

[1] $\eta^2 = .712$

**Table 6:** Correlations between baseline habituation and personality factors (Pearson Correlation). N= 31

| | Baseline Habituation |
|---|---|
| Extraversion | -.066 |
| Neuroticism | -.015 |
| Openness | -.176 |
| Conscientiousness | .029 |
| Agreeableness | .237 |
| Impulsivity | -.128 |

**Table 7:** Statistical Analysis of Effects of high/low trait impulsivity on baseline ASR amplitudes (Mixed Design ANOVA).

| Source of Variance | Type III Sum of Squares | df | df2 | *Mean Squares* | *F* | *Sig.* |
|---|---|---|---|---|---|---|
| Block | 111317.217 | 1 | 30 | 111317.217 | 52.251 | .000[1] |
| Block* Trait Impulsivity | 727.988 | 1 | 30 | 727.988 | .342 | .563 |

Note:

[1] $\eta^2 = .635$

## 8. List of figures

**Figure 1:** Mean ASR amplitudes across pulse-alone blocks in both sessions.

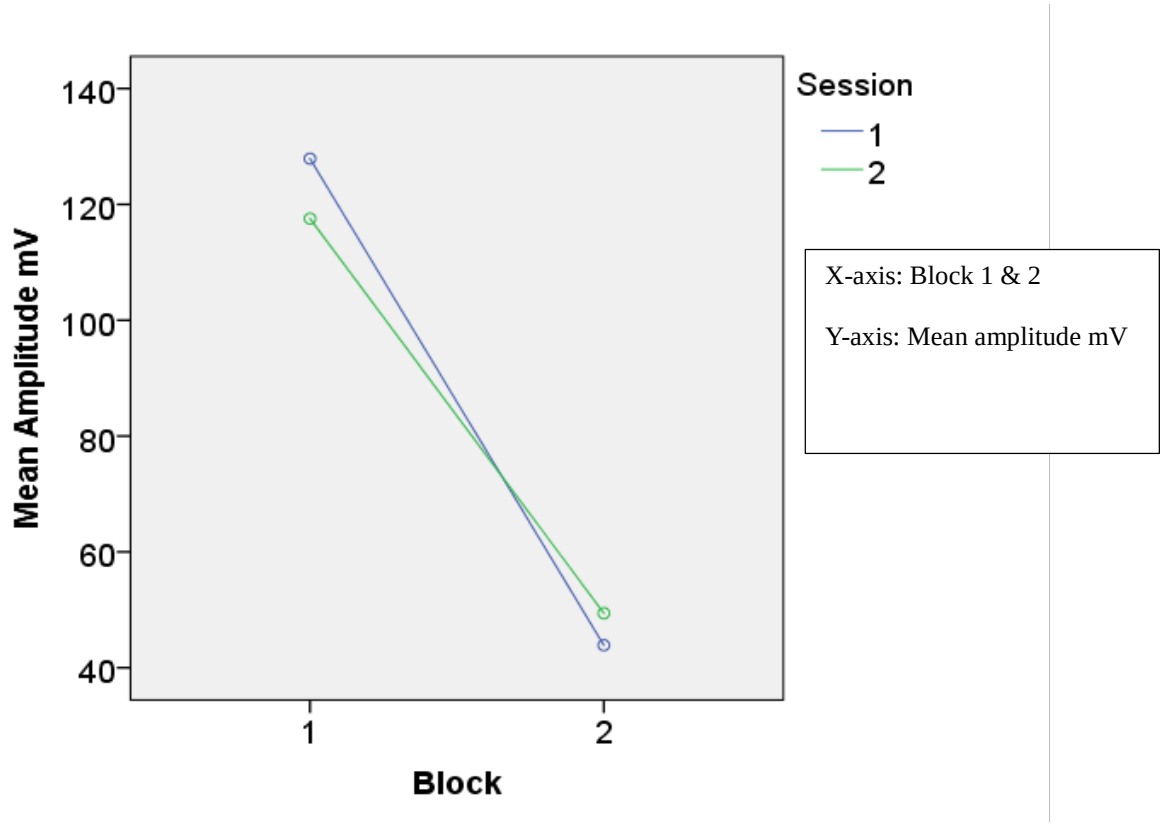
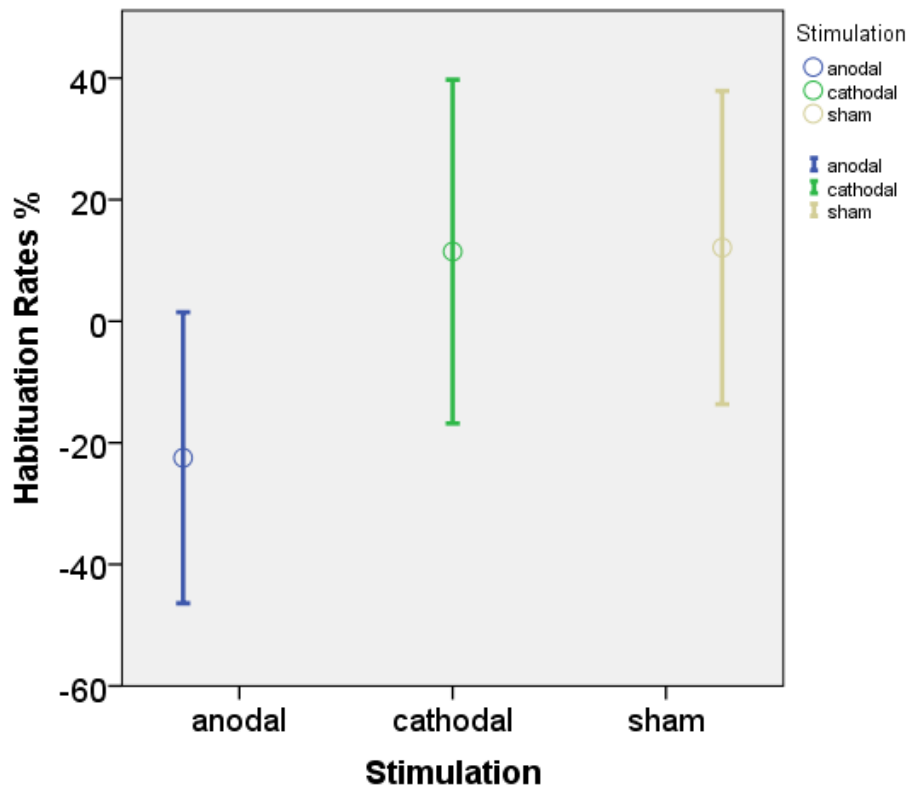


**Figure 2:** Habituation rates across stimulation conditions

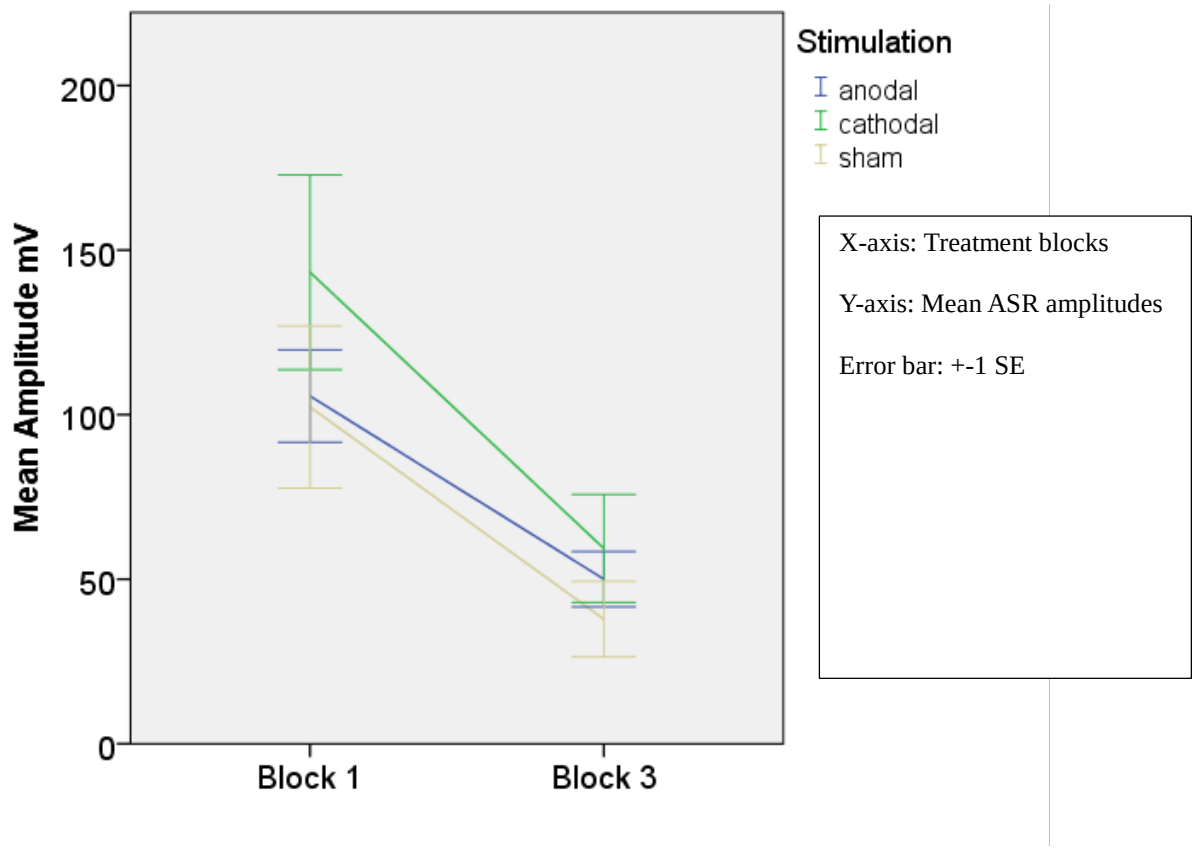



X-axis: Stimulation conditions

Y-axis: Habituation rates

Error bar: +-1 SE

**Figure 3:** Mean ASR amplitudes of pulse-alone blocks across stimulation conditions.



## Education

| | |
|---|---|
| 2000-2002 | Pre-school teacher training, Speyer |
| 2002-2005 | Abitur at Abendgymnasium am Holstenglacis, Hamburg |
| 2007- 2016 | Diplomstudium Psychology<br>Area of specialization: Biological, Clinical and Applied Developmental Psychology |

## Professional Experience

| | |
|---|---|
| 2000-2002 | Pre-school teacher at Evangelische Diakonissenanstalt, Speyer<br>Educating children from 3-6 years old |
| 2002-2006 | Stagehand at U-Need GmbH, Hamburg<br>Construction of stages and technical support |
| 07/2008-10/2008 | Internship at Deutsche Börse AG, Frankfurt<br>Member services of the Deutsche Börse AG |
| 2007- | Trainer at the sociotherapeutic center “Pappel”, Vienna<br>Support of clients with mental disorders |