# Modification of inhibitory control via antisaccade training in spider phobia

## Statistical Analysis Plan (SAP)

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## SAP responsibilities

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## 1. Introduction

### 1.1 Background

Specific phobia is a highly prevalent anxiety disorder (prevalence: 1.5% to 14.4% in adults [1]). Specific phobia is characterized by excessive fear of a specific object (e.g. spiders) or a specific situation and their avoidance [2]. Despite effective treatments [3], about one-third of patients do not respond to first-line therapies [4, 5].

Impaired inhibitory control was recently discussed as a potential factor that could contribute to the risk and maintenance of anxiety in general [6, 7]. A widely used tool to assess inhibitory control is the antisaccade task [8]. The latency of correct antisaccades constitutes a measure of efficiency, while the error rate indicates the effectiveness of inhibitory control [9]. In previous studies, antisaccade training has successfully improved antisaccade performance (latencies and/or error rates) in clinical and non-clinical samples [10–13]. For example, antisaccade training employing disorder-related stimuli (pictures of high-caloric food) led to a reduction in error rates and a lower number of binge eating episodes in a sample of patients with binge eating disorder [10].

Though inhibitory control is considered a factor in anxiety, the potential of antisaccade training as an intervention for anxiety disorders has not yet been explored. Further, it is unclear, whether the effects of antisaccade training employing disorder-related stimulus material [10] are specific to changes in antisaccade performance in response to disorder-related stimuli or influence antisaccade performance irrespectively of employed stimuli.

This SAP refers to the intervention part of an overarching clinical study on antisaccade performance in patients with spider phobia, which was preregistered with ISRCTN (Study ID: ISRCTN12918583; Registered on 28th February 2022). A SAP on planned analyses of data obtained during the baseline assessment has previously been preregistered (see SAP_1: ISRCTN12918583 SAP_Baseline v1.0 30Nov2022.pdf). Recruitment of participants is ongoing. Preliminary analyses of baseline data on a sub-sample have already been performed.

### 1.2 Objectives

The aim of the interventional study part is to pilot the modifiability of inhibitory control through a phobia-related antisaccade training in patients with spider phobia (SP) and healthy controls (HC).

First, we aim to investigate whether an antisaccade training employing phobia-related stimuli will change antisaccade performance. We hypothesize that an antisaccade training (compared to prosaccade training) will increase antisaccade performance.

Second, we aim to explore whether putative training effects differ between patients with SP and HC.

Third, we aim to explore, whether putative training effects are specific for the trained (phobia-related) type of stimuli. In case of stimulus-specific training effects, one would expect stronger gains in antisaccade performance to phobia-related compared to neutral stimuli. If the subjective emotional relevance of the trained phobia-related stimuli (SP > HC) influences training effects, interactions of the factors training condition, group, time, and stimulus material would be expected.

Fourth, we aim to investigate whether the antisaccade training reduces avoidance behavior in SP. We also test whether individual changes in antisaccade performance predict avoidance behavior above and beyond putative training induced changes on a group level.

## 2. Methods

### 2.1 Study Design

Patients with SP and HCs, all aged between 18 and 65 years, will be assessed regarding training-induced changes in inhibitory control functions via an emotional antisaccade task, using phobia-related and neutral stimulus material (schematic pictures of spiders and flowers).

We employ a 2 (training condition: antisaccade vs. control) × 2 (group: SP vs. HC) × 2 (time: baseline vs. post-assessment) × 2 (stimulus material: phobia-related vs. neutral) design, with training condition and group as between-subject factors and time and stimulus material as within-subject factors.

Outcome measures (see 5) will be obtained before (baseline assessment) and after (post-assessment) an antisaccade or the control training (prosaccade training).

#### 2.1.1 Training

Antisaccade Training: Phobia-related visual stimuli (pictures of spiders) will be presented on a screen in the left or right peripheral visual field. Participants are instructed to look at the mirrored position on the screen. The duration of this training is 15 minutes including short breaks.

Prosaccade Training: Phobia-unrelated visual stimuli (pictures of neutral objects) will be presented on a screen in the left or right peripheral visual field. Participants are instructed to look at the presented stimulus. The duration of this training is 15 minutes including short breaks.

### 2.2 Randomization

Patients and healthy controls are randomly assigned to the two training conditions using a block randomization scheme to guarantee equal group sizes.

### 2.3 Sample Size

Based on a study using antisaccade training and the antisaccade task in clinical samples [10], we calculated an a-priori power analyses using G*Power 3.1 [14] for a mixed measures ANOVA (Analysis of Variance) to detect large effect sizes (Cohen´s $f$ = .40, $\alpha$ = .05, power = .85) in our primary outcome (i.e. antisaccade latencies) for the training effect. Results indicated a required total sample size of 59 participants (30 per group).

### 2.4 Timing of final analysis

Data will be analyzed after completion of final baseline analyses (see SAP 1).

## 3. Statistical principles

### 3.1 p-Values and Effect Size

For all analyses, significance levels will be set to $p$ = .05. As an effect size for ANOVAs, partial-Eta$^2$ ($\eta_p^2$) will be used. For multiple regression, Cohens $f^2$ will be used.

### 3.2 Missing Data and Outliers

Information on missing data and outliers in primary and secondary outcome measures can be found in the SAP on baseline data (see SAP 1, section 3.2).

## 4. Trial population

### 4.1 Eligibility criteria

A list of eligibility criteria can be found in the study registration (Study ID: ISRCTN12918583).

### 4.2 Recruitment

A CONSORT-Flow diagram will be presented in the manuscript.

### 4.3 Sample characteristics

Sociodemographic sample characteristics will be presented separately for groups (SPs and HCs) and training conditions (antisaccade training, control training). Variables showing expected differences of the factor group, as well as (unexpected) effects of the factor training in the baseline assessment will be identified using ANOVAs and chi-square tests.

## 5. Outcome measures

### 5.1 Primary outcome measure

The primary outcome will be antisaccade latency, measured in milliseconds (ms). Antisaccade latency is defined as the time between stimulus onset and the initiation of a correct antisaccade. Antisaccade latency reflects inhibitory control efficiency.

### 5.2 Secondary outcome measure

The secondary outcome will be antisaccade error rate in percent (%). Antisaccade error rate is defined as the proportion of trials, in which an individual performs an erroneous prosaccade towards the presented stimulus. Antisaccade error rate reflects inhibitory control effectiveness.

### 5.3 Measurement of Avoidance behavior

Avoidance behavior in response to a real-life spider will be defined as the final distance between the participant and the spider in centimeters (cm) during the BAT (for a detailed description of the BAT please refer to the work of Schwarzmeier and colleagues [15]).

## 6. Analyses

All analyses will be conducted as indicated and required statistical assumptions will be checked before conducting the respective analyses. In case of (unexpected) baseline differences of the factor training in relevant sample characteristics (see 4.3), we will control for the respective variables in the statistical analyses.

### 6.1 Analysis of Primary Outcome

To investigate inhibitory control efficiency (indexed by antisaccade latencies) a 2×2×2×2 mixed measures ANOVA, employing training condition (antisaccade training vs. control) and group (SP vs. HC) as between-subject factors, and time (baseline vs. post-assessment) and stimulus material (phobia-related vs. neutral) as within-subject factors, will be conducted.

The hypothesis that an antisaccade training (compared to prosaccade training) will increase antisaccade performance will be indicated by a significant interaction of training condition × time with reduced latencies in both groups.

Group-specific effects of the training would be indicated by a significant three-way interaction of training condition x group x time.

To explore whether putative changes are specific for the trained (phobia-related) type of stimuli, we will explore whether these interactions will be modulated by the factor stimulus material (phobia-related vs neutral).
Respective Bonferroni-corrected post-hoc tests will be conducted to further delineate significant interactions.

### 6.2 Analysis of Secondary Outcome

These analyses will be repeated with the secondary outcome (antisaccade error rates) as the dependent variable.

## 6.3 Analysis of Avoidance Behavior

To explore whether the antisaccade training reduces avoidance behavior, we will set up a hierarchical regression model, employing the BAT baseline scores and the training condition (antisaccade training vs. control) as predictors and the BAT post-assessment scores as the outcome measure (basic model). In a second step, this basic model will be extended (see below).

- Model 1: Overall changes in antisaccade latencies
  To test whether individual changes in antisaccade latencies predict avoidance behavior above and beyond putative training-induced changes, the basic model will be extended by adding the overall change in antisaccade latencies (post – baseline) as a predictor.
- Model 2: Overall changes in antisaccade error rates
  To test whether individual changes in antisaccade error rates predict avoidance behavior above and beyond putative training-induced changes, the basic model will be extended by adding the overall change in antisaccade error rates (post – baseline) as a predictor.

In case of significant modulatory effects of stimulus material on antisaccade latencies (see 6.1) and/or antisaccade error rates (6.2), we will additionally test the following models as exploratory analyses, that include stimulus-specific difference scores: Therefore, change scores of antisaccade latencies and/or antisaccade errors in the neutral condition (post – baseline) will be subtracted from change scores in the phobia-related condition (post – baseline).

- Model 3: Changes in antisaccade latencies to phobia-related stimuli
  To test whether individual changes in antisaccade latencies to phobia-related stimuli predict avoidance behavior above and beyond putative training-induced changes, the

basic model will be extended by adding the differences scores in antisaccade latencies ($\text{phobia-related}_{\text{post-baseline}} - \text{neutral}_{\text{post-baseline}}$) as a predictor.

- Model 4: Changes in antisaccade error rates to phobia-related stimuli
  To test whether individual changes in antisaccade error rates to phobia-related stimuli predict avoidance behavior above and beyond putative training-induced changes, the basic model will be extended by adding the differences scores in antisaccade error rates ($\text{phobia-related}_{\text{post-baseline}} - \text{neutral}_{\text{post-baseline}}$) as a predictor.

In case of significant effects of change scores of antisaccade performance, exploratory multilevel models will be employed to examine the specific contribution of antisaccade performance at baseline and post assessment.

### 6.4 Statistical Software

Analyses will be performed using RStudio (Version 2023.03.0+386; R-4.2.2).

## References


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