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Statistical Analysis Plan (SAP)

English Title of the Study: **Investigation of Possible Effects of a Lifestyle Product in a Double-blind Pre- Post-Between-Groups Study**

German Title of the Study: Untersuchung möglicher Effekte eines Lifestyle-Produktes und Zusammenhänge von Persönlichkeits- und Intelligenzfaktoren mit paranormalen Überzeugungen in einer doppel-blinden Pre-Post-Between-Groups Studie

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SIGNATURE PAGE

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Abbreviations

EDA	Electrodermal Activity
EEG	Electroenzephalography
ECG	Elecrocardiography
FAA	Frontal Alpha Asymmetry
WHO	World-Health-Organisation
EHS	Electromagnetische hypersensibility
HRV	Heart rate variability
HF	High Frequency
LF	Low Frequency
EO	Eyes open
EC	Eyes closed
PSQI	Pittsburgh Sleep Quality Index
WMT-2	Vienna Matrices-Test –2
PANAS	Positive and Negative Affect Schedule

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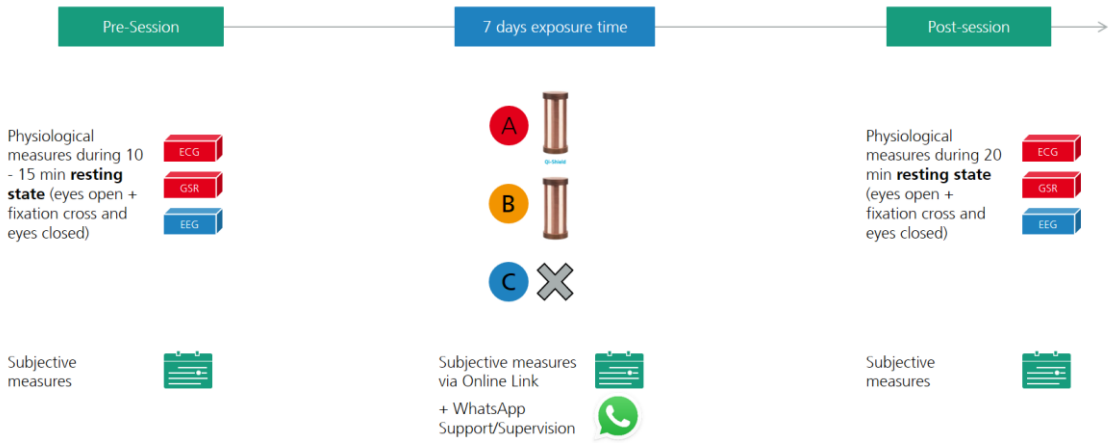
1. Introduction

The aim of the study is to investigate possible effects of the lifestyle product "Qi-Shield" on a subjective and (neuro-)physiological level.

This statistical analysis plan (SAP) will give more detailed descriptions of the endpoints in the study and the corresponding analyses.

2. Study design

Participants will be recruited through the participant pool of the research institute and received a monetary reward to compensate for time and travel costs. The study is a double-blind pre-post-between-groups design with an exposure time of 7 days between the two sessions. 90 test persons are to be assigned to the three groups. Two groups receive an intervention with (A) the real product (active treatment arm) and (B) a sham product without effectiveness representing the placebo treatment arm. A third group receives no intervention as a further control (no treatment arm). Regarding the effects of the product, we are particularly interested in effects on well-being, stress perception and the sleep quality as well as influencing factors like personality and beliefs. We will use established questionnaires and scales as well as (neuro-)physiological methods comprising electroencephalography (EEG), electrocardiogram (ECG) and skin conductance level measure (electrodermal activity, EDA) during a 20 mins resting state measure with alternating eyes open and closed. During the exposure time, participants are asked to rate their subjective well-being and stress on a daily basis via an online survey.



2.1 Sample size calculation

For the calculation of the Falling Number, a power analysis with the software G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) was calculated for an analysis of variance with measurement repetition and between-subject factor assuming a normal distribution. With a small to medium effect (Cohen's d = 0.35), an alpha level of 0.05 (Bortz & Döring, 2006; Eid, 2010), a statistical power of 80% and an assumed strong correlation between measurements (r=0.8), the resulting case number is N=90. For both neurophysiological and subjective responses, the 3 groups with n=30 each are statistically compared.

3. Aims and objectives

To study the effects of the product, we investigate neuro- and peripheral physiological correlates during rest as well as subjective measurements regarding subjective well-being, perceived stress and resilience, positive and negative emotional states and sleep quality.

4. Outcome Measures

This section will present the outcomes investigated to answer the study aims and objectives. The analyses are described in section 6 Analyses.

4.1 Primary Outcome Measure

Adapted Pittsburgh Sleep Quality Index (PSQI), Buysse et al. (1989)

Hypothesis Sleep Quality: Lower values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

WHO-5, WHO, Psychiatric Research Unit

Hypothesis Subjective well-being: Higher values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

State Trait Anxiety Inventory (Laux, Glanzmann, Schaffner & Spielberger (1981)

Hypothesis STAI: Lower values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

Positive and Negative Affect Schedule, PANAS, Breyer & Bluemke (2016)

Hypothesis PANAS: Higher values in the post - pre session delta for positive adjectives and lower values in the post - pre session delta for negative adjectives in the real device group compared to the sham device group and no intervention group.

Adapted Perceived Stress Scale, Schneider, Schönfelder, Domke-Wolf & Wessa (2020)

Hypothesis Perceived Stress: Lower values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

Brief Resilience Scale, Chmitorz et al (2018)

Hypothesis Resilience: Higher values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

EEG Alpha band power and connectivity

Hypothesis: Higher alpha band power and functional connectivity for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

EEG Beta band power and connectivity

Hypothesis: Higher beta band power and functional global connectivity for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group

EEG: Frontal alpha band asymmetry (right side activity)

Hypothesis: Lower right side alpha band power for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

EEG: Frontal theta/beta band ratio

Hypothesis: Higher frontal theta/beta band ratio for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group

EDA: number of individual phasic responses and summed amplitude of phasic responses

Hypothesis: Lower number of individual phasic responses and summed amplitude of phasic responses for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

ECG: Low frequency response in the heart rate variability

Hypothesis: Less low frequency responses in the heart rate variability for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

ECG: High frequency response in the heart rate variability

Hypothesis: Increased high frequency responses in the heart rate variability for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

ECG: Standard deviation of normal-to-normal intervals (SDNN) and heart rate

Hypothesis: Increased standard deviation of normal-to-normal intervals (SDNN) and heart rate for the delta between pre- and post-session in the real device group compared to the sham device group and no intervention group.

Satisfaction with Life Scale, Janke & Glöckner-Rist (2012)

Hypothesis Life satisfaction: Higher values in the post - pre session delta for the real device group compared to the sham device group and no intervention group.

4.2 Secondary Outcomes

Complementary and Alternative Medicine (CAM) Health Belief Questionnaire, Lie & Boker, 2004

Explorative Hypothesis: Higher values for participants exhibiting a placebo effect of the intervention. Values of the CAMHBQ are positively correlated with values in the Revised Paranomal Belief Scale and Adapted Paranormal Experience Scale and negatively correlated with responses in the Vienna matrix test. The Complementary and Alternative Medicine (CAM) Health Belief Questionnaire provides a control measurement for the comparability of the groups.

Adapted Paranormal Experience Scale, Aubeck, 1989

Explorative Hypothesis: Higher values for participants exhibiting a placebo effect of the intervention. Values of the Adapted Paranormal Experience Scale are positively correlated with values in the Revised Paranomal Belief Scale and Complementary and Alternative Medicine (CAM) Health Belief Questionnaire and negatively correlated with responses in the Vienna matrix test. The Adapted Paranormal Experience Scale provides a control measurement for the comparability of the groups.

Revised Paranomal Belief Scale, Tobacyk, 2004

Explorative Hypothesis: Higher values for participants exhibiting a placebo effect of the intervention. It is positively correlated with values in the Adapted Paranormal Experience Scale and Complementary and Alternative Medicine (CAM) Health Belief Questionnaire and negatively correlated with responses in the Vienna matrix test. The Revised Paranomal Belief Scale provides a control measurement for the comparability of the groups.

Vienna matrix test -2, Formann, Waldherr & Piswanger, 2011

Explorative Hypothesis: Higher values are negatively correlated with the paranormal belief scale and openness for paranormal and alternatives beliefs and experiences. The Vienna matrix test provides a control measurement for the comparability of the groups.

Short version of the Big 5 Inventory, Rammstedt & John, 2005

Explorative Hypothesis: Higher values in the factor openness to new experience are positively correlated with the paranormal belief scale and openness for paranormal and alternatives beliefs and experiences and negatively correlated with the Vienna matrix test. The short version of the Big 5 provides a control measurement for the comparability of the groups.

Karolinska Sleepiness Scale, Akerstedt & Gillberg, 1990

The KSS provides a control measure before the 20 min resting state recording. Participants revealing values > 8 will be excluded from the analysis.

5. Analyses

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD) and skewed distributions by the median and interquartile range (IQR). Binary and categorical variables will be presented using counts and percentages. All data analyses will be performed with custom written or adapted scripts in pythonTM, JASP 0.13.1 (JASP, 2020) and IBM® SPSS® Statistics 20.

For the estimation of the power spectral density (PSD), we will apply fast fourier transformation (FFT) to the EEG resting state data. To reduce the variability of the spectral estimates a Welch's method will be applied. For the statistical analysis the PSD data will be transformed to a dB scale. Since PSD of the scalp EEG can vary between different participants due to several factors (anatomical, age and gender characteristics) the data will be further normalized (z-score) before the statistical comparisons can be done. Furthermore, we will explore whether spectral smoothing, according to a multi-tapering approach, of the PSD data has any influence on the statistical outcome.

To estimate functional connectivity (deviations from statistical independence between EEG time series) of the resting state EEG data we will explore several methods which are insensitive to volume conduction properties. The estimation will be done in the frequency domain (using fft and multi-tapering, see above). Here, several methods have been established to distinguish true physiological neuronal interactions from volume conduction effects. In our study, we will compare the 3 most dominant methods reported in the cognitive neuroscience literature, which are: the imaginary part of the coherence function (iCOH), Nolte et al. 2004 and it's corrected version as suggested by Ewald et al. (2012), corrected version of the iCOH function (ciCOH), the Phase-Locking Value (PLV), Lachaux et al. (1999) and it's corrected version as suggested by Bruña et al. (2018) corrected imaginary PLV (icPLV), and the Phase Lag Index (PLI), Stam et al. (2007) and it's corrected version as suggested by Vinck et al. (2011) Weighted Phase Lag Index (WPLI).

From the resting ECG measurements we will calculate heart rate variability (HRV) measures. First, the ECG is processed to acquire the inter-beat interval (IBI –the inverse of heart rate). For this purpose, the ECG is band-pass filtered between 5 and 15 Hz. Next, R-Peaks are detected following Pan and Tompkins method. Next, the IBI semi-time series is transformed into a time series. This is done by interpolating (quadratic spline interpolation) consecutive IBIs and then resampling the data to a particular sampling frequency. In this way, the IBI is transformed to heart rate (indicated heart beats per min) and can be used for further statistical analysis. From the heart time series, we will extract several statistical measures for the group statistical comparisons such as: the max, min and mean of the Amplitude, the skewnees, kurtosis, and std of the data, and the RMSSD (square root of the mean of the sum of successive differences between adjacent RR intervals); SDNN (standard deviation of the RR intervals); MeanNN (mean of the RR intervals); SDSD (standard deviation of the successive differences between RR intervals). We will furthermore characterize the heart rate variability in the frequency domain using fft. Here, low frequency band (0.04-0.15Hz), high frequency band (0.15-0.4Hz) and the ratio of the two will be compared.

For the analysis of the measured EDA resting state signal, the data will be decomposed into smaller phasic responses (individual rapid spontaneous responses – usually related to certain stimuli) and tonic components (longer lasting basic skin resistance level). From these two components several physiological measures will be extracted for the group statistical comparison such as: the number of individual phasic responses, summed amplitude of phasic responses; minimum, maximum and average of phasic responses; integral of phasic responses; tonic state of electrical conductivity.

For all the calculated (neuro-)physiological measures of the resting state we will do the statistical comparison among the groups. In particular, we will use the delta of the outcomes off the pre- and postsession for the neurophysiological and subjective measurements. Either parametric or non-parametric statistical tests depending on the violation of the assumptions (i.e., normal-distribution of the dependent factor examined by the Shapiro-Wilk test) are used. *P*-values are corrected for multiple comparisons using the false discovery rate (FDR) with the Benjamini-Hochberg method.

6. Missing data

Participants with missing data are excluded for the respective outcome analysis.

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References

Bruña R, Maestú F, Pereda E. Phase locking value revisited: teaching new tricks to an old dog. J Neural Eng. 2018 Oct;15(5):056011. doi: 10.1088/1741-2552/aacfe4 . Epub 2018 Jun 28.

Ewald, A., Marzetti, L., Zappasodi, F., Meinecke, F.C., Nolte, G., 2012. Estimating true brain connectivity from EEG/MEG data invariant to linear and static transformations in sensor space. NeuroImage 60, 476–488. doi:10.1016/j.neuroimage.2011.11.084

Jiapu Pan and Willis J. Tompkins. A Real-Time QRS Detection Algorithm. In: IEEE Transactions on Biomedical Engineering BME-32.3 (1985), pp. 230–236.

Lachaux JP, Rodriguez E, Martinerie J, Varela FJ. Measuring phase synchrony in brain signals. Hum Brain Mapp. 1999;8(4):194-208.

Nolte, G., Bai, O., Wheaton, L., Mari, Z., Vorbach, S., Hallett, M., 2004. Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin. Neurophysiol. 115, 2292–2307. doi:10.1016/j.clinph.2004.04.029

Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp. 2007 Nov;28(11):1178-93.

Vinck M, Oostenveld R, van Wingerden M, Battaglia F, Pennartz CM. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. Neuroimage. 2011 Apr 15;55(4):1548-65. doi: 10.1016/j.neuroimage.2011.01.055 . Epub 2011 Jan 27.