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MASTERARBEIT

Titel der Masterarbeit

„Cognitive and Physical Performance Changes Caused by Expectation of Enhancement: The Power of Placebo in Healthy Individuals“

verfasst von

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Ei Possen! Das ist nur zum Lachen;
Sei nur nicht ein so strenger Mann!
Sie muß als Arzt ein Hokuspokus machen,
Damit der Saft dir wohl gedeihen kann.

Mephistoles, Goethe's Faust

If I have seen further it is by standing on the shoulders of giants.

Isaac Newton, adapted from Bernard of Chartres

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This project wouldn't have been possible without the help of Grega Repovs. Thanks for hours of programming and repeated EEG data analyses.

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Abstract

This empirical thesis aims to test if placebo-induced expectation of enhancement actually leads to physical and cognitive performance increase. Healthy young volunteers (n = 21) performed short tests of physical (muscle force and timed workout) and cognitive function (auditory oddball test) at two sessions, which were three days apart. In each session two measurement runs were separated by an intermission, when a vitamin C tablet was given and announced either as a stimulant with a perceptible calorigenic side effect or as a control substance. During the cognitive task sessions electroencephalogram (EEG) was recorded to assess event related potential (ERP) P3 mean amplitude and latency, as well as myoelectrical activity of active muscles (electromyogram) and autonomic nervous system tone (heart rate and heart rate variability). At the end of each session individual feedback about perceived performance during the tasks was recorded. After the second session, participants filled in a 44-item BFI personality questionnaire.

The results showed significant placebo effect on total leg workout ($p = 0.004$) but not on maximal handgrip force ($p = 0.39$). There was no difference in oddball test performance between runs and sessions ($p = 0.911$), but a significant session x run interaction ($F(1,21) = 5.8$; $p = 0.025$) in EEG measures revealed a decrease in P3 mean amplitude after the “stimulant” but not after the control substance. Given the theoretical background of P3 functionality (Luck, 2005), this amplitude decrease could be interpreted as less cognitive resources needed to perform the oddball task on the same performance level after placebo treatment. Neither autonomic nervous tone ($p > 0.23$) nor myoelectrical activity of handgrip flexors ($p > 0.37$) seemed to be significantly modulated by placebo treatment. Perceived oddball task accuracy correlated with actual performance in oddball test ($p < 0.05$), other correlations between perceived and tested performance did not reach significance (all $r < 0.25$, $p > 0.14$). Moreover, perceived performance and motivation did not change significantly after treatment in both sessions (all $p > 0.13$). Correlations between BFI personality scores for agreeableness ($r(19) = 0.40$, $p = 0.036$) and conscientiousness ($r(19) = 0.39$, p 0.040)

and placebo effect on total leg workout were significant.

In summary, expectation of performance enhancement yielded increased physical workout but no change in active force, revealing motivation-dependent increase in endurance, but no change in core muscle strength. Sustained mental performance with a concurrent reduction in cognitive resource allocation may suggest reliance of subjects on stimulant effect during cognitive task, where feedback was not immediately available.

Zusammenfassung

Die vorliegende experimentelle Arbeit beschäftigt sich mit der Frage, ob und mit welchem Ausmaß sich die geistige und körperliche Leistungsfähigkeit junger und gesunder Probanden mit Hilfe von Placebo Behandlungen steigern lässt und welche Faktoren diese etwaige Leistungssteigerung modulieren könnten. Freiwillige kaukasische Probanden (n = 21) unterzogen sich zwei kurzen körperliche und einem kognitiven Leistungstest, welche im genaueren die maximale Muskelkraft der Handkontraktion, die Muskelgesamtleistung des musculus quadriceps und die geistige Konzentrationsfähigkeit mit Hilfe eines akustischen „Oddball“ -Tests feststellten. Das Experiment bestand aus zwei Einheiten, die an getrennten Terminen stattfanden. In jeder Einheit wurden die drei Leistungstests in je zwei Messungen ausgeführt, welche durch eine kurze Pause unterbrochen wurden. Während der Pause wurde den Probanden eine wasserlösliche Vitamin C Tablette verabreicht, einmal mit der Information, es handle sich hierbei um Vitamin C und einmal proklamiert als eine starke leistungssteigernde Substanz unter dem Namen “PEpX”, mit einer merklichen wärmeerzeugenden Nebenwirkung. Während der kognitiven Leistungstests wurden Elektroenzephalogramm (EEG) Messungen durchgeführt, um ereignisbezogene Potentialdifferenzen (event related potentials, ERP), besonders die P3 Komponente, sowie mögliche Einflüsse der Placebo Behandlung auf das autonome Nervensystem zu evaluieren. Am Ende der zweiten Messung wurde ein kurzer Fragekatalog zur subjektiven Einschätzung der eigenen Leistung und etwaiger Veränderungen in der zweiten Hälfte nach der Behandlung ausgefüllt und am Ende der zweiten Einheit absolvierten die Probanden den “Big Five Inventory” (BFI) Persönlichkeitstest mit 44 Fragen.

Die Ergebnisse zeigen einen signifikanten Placebo Effekt auf die Gesamtleistung des Quadriceps ($p = 0.004$), jedoch keinen Effekt auf die maximale Muskelkraft der Handkontraktion ($p = 0.39$). Es gab ebenfalls keine signifikante Änderung der Genauigkeit im kognitiven Oddball Test weder innerhalb noch zwischen den Einheiten ($p = 0.911$), jedoch zeigte die EEG Analyse eine signifikan-

te Interaktion zwischen Experimentbedingung und Messzeitpunkt ($F(1, 21) = 5.8$; $p = 0.025$) und deutet somit auf eine Verringerung der durchschnittlichen P3 ERP Amplitude hin, speziell nach der Placebo- und nicht nach der Kontrollbehandlung. In Bezug auf die in der Literatur beschriebene Funktion der P3 Komponente (Luck, 2005) lässt sich dieser Abfall als Verringerung der Benötigten kognitiven Ressourcen des Arbeitsgedächtnis deuten, welche auf eine indirekte Leistungssteigerung schließen lassen könnte. Weder der Tonus des autonomen Nervensystems ($p > 0.23$), noch die myoelektrische Muskelaktivität ($p > 0.37$) änderte sich signifikant nach der Placebo Behandlung. Die wahrgenommene Leistung der Probanden im Oddball Test korrelierte mit der tatsächlich gemessenen in beiden Schwierigkeitsstufen ($p < 0.05$), andere Korrelationen zwischen wahrgenommener und tatsächlicher Leistung waren jedoch nicht signifikant (alle $r < 0.25$, $p > 0.14$) und es konnte auch keinen signifikanter Placebo Effekt auf die Wahrnehmung der eigenen Leistung vor und nach der Behandlung gemessen werden (alle $p > 0.13$). Korrelationen zwischen den vom BFI errechneten Persönlichkeitswerte für ‘Verträglichkeit’ ($r(19) = 0.40$, $p = 0.036$) und für ‘Gewissenhaftigkeit’ ($r(19) = 0.39$, $p = 0.040$) mit dem Placebo Effekt auf die Gesamtbelastbarkeit der Quadriceps Muskeln waren signifikant.

Die Ergebnisse zeigen insgesamt, dass die Erwartung von Leistungssteigerung, ausgelöst durch Placebo Behandlung, eine tatsächliche Leistungssteigerung in muskulärer Gesamtbelastbarkeit, aber nicht in maximaler Muskelkraft hervorrufen konnte. Eine mögliche Interpretation dessen ist ein motivationsabhängiger Anstieg der muskulären Ausdauer durch körpereigene Reserven, welcher jedoch keinen Einfluss auf die maximale Amplitude der Muskelkraft hat. Gleichbleibende kognitive Leistung bei gleichzeitiger Reduktion der Allokation kognitiver Ressourcen könnte darauf hinweisen, dass sich die Probanden während des Oddball Tests auf die leistungssteigernde Wirkung des Placebos verließen, da für sie währenddessen ihr eigenes Leistungsniveaus nicht feststellbar war.

List of Abbreviations

1RM	One repetition maximum [kg]
BFI	Big five inventory
D	Distractor
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
ERP	Event related potentials
fMRI	Functional magnetic resonance tomography
HG	Hand grip
JND	Just noticeable difference [Hz]
LE	Leg extension
OB	Oddball
PE	Placebo effect
PEp	Performance enhancing placebo
PEpX	Performance enhancing placebo experiment
PET	Positron electron tomography
RCT	Double-blinded, randomized, placebo-controlled trials
RMS	Root mean square
T	Target

1.Introduction

1.1 Definition

To understand the effects of a placebo, one should first define the term placebo itself: “Placebo” origins from the Latin verb "placere", which means "to like" or "to please". The derived expression "placebo" then can be translated with "I shall please" or "I will be pleased". Nowadays, placebo is employed mostly in clinical environments, usually as a “pharmacologically inert preparation, prescribed more for the mental relief of the patient than for its actual effect on a disorder” and is conventionally applied in clinical trials as “an inert or innocuous substance […] testing the efficacy of another substance (a drug)” (Merriam-Webster Medical Dictionary, 2013). A placebo effect in turn, defines the amount of improvement such a placebo treatment would account for.

However, an increasing body of literature indicates that “placebos are not inert substances, as thus far believed” (Benedetti et al., 2011). The true nature of placebo actually resembles more to the verbatim Latin definition, which highlights the pivotal role of the own conscious expectation next to all other additional effects caused by the treatment. Hence, a better definition might be: placebos are verbal suggestions given along with the treatment or any other cues of clinical benefit. These cues, coming from the right psychosocial context of the treatment, then lead to positive expectations via anticipating a beneficial treatment outcome.

Indeed, there is ample support that positive expectations actually do lead to a more positive treatment outcome. In the past decades, research has discovered a great variety of placebo effects, with different modes of action, such as modulation of anxiety pain experience activity of the reward system and also with involvement of learning phenomena such as Pavlovian conditioning and cognitive as well as social learning (Benedetti et al. 2011).

1.2 Effect size of the placebo effect

But how much, if at all, does placebo intervention really differ from a no-treatment condition? Since the first half of the 20th century double-blinded, randomized, placebo-controlled trials (RCT) have been established as the gold standard of evidence based medicine. Therefore, there has been a growing body of clinical placebo knowledge, investigating how well medication works in contrast to placebo, with a focus on clinical patients. However, the actual size of effects caused genuinely by placebo remains largely unknown.

The immanent question about the effect size of placebo treatments has been addressed by several meta-studies comparing placebo treatment outcomes across many clinical trials. In 1955, Beecher's first meta-study showed notable placebo effects across several conditions, such as pain, anxiety and coughing with an average of 35.2% in the patient population being satisfactorily relieved only by placebo treatment. Another meta-study on clinical success of antidepressants vs. placebo treatment had an even more drastic outcome: It indicated that only a quarter of patient responses were actually due to the pharmacological effect of the antidepressant drug, another quarter was due to the natural history of depression and the other half was due to the placebo effect (Kirsch & Sapirstein, 1998). However, the methodology of both studies has been criticized. On the other hand, other meta-analyses (Hróbjartsson & Gøtzsche, 2001) claim to have found that „ […] little evidence in general that placebos had powerful clinical effects". At this point one has to note that results drawn from such meta-studies are in general highly dependent on the aim and quality of original studies or trials selected. In medical trials, placebo has been mostly exploited focusing on the evaluation of substances or treatments on patient populations in comparison to treatment with inert substances, such as saline solutions, yet do trials neither explain what placebo actually is, nor how it works (Benedetti et al., 2008). Using only RCT with patient populations in order to determine the effect size of placebo treatment, therefore might pose some problems. Firstly, a third no-treatment group should control for possible confounds of the effect size by changes in the natural history and other influences.

However, this poses an ethical problem, because it would mean to consciously withdraw patients from their treatment. Secondly, even with a no-treatment group included, the purpose of medical trials is usually not to determine the effect size of the whole psychobiological placebo phenomenon, but to measure the effect size of a certain drug, hence it might be precarious to determine effect sizes from such measurements.

Notwithstanding the importance of inert substances in clinical trials, their major focus, the inert substance itself, again does not comprise the real meaning of placebo (Moerman, 2002). The whole psychobiological placebo response comes from positive social stimuli, such as verbal suggestions of clinical benefit and rituals of the therapeutic act.

1.3 Psychological Mechanisms

There are many psychological mechanisms, which contribute to placebo effects, including learning (conditioning and conscious), expectations, somatic focus, reward, anxiety reduction and motivation (Price et al., 2008; Benedetti, 2008). Two principal mechanisms have become apparent: classical conditioning and expectancy.

1.3.1 Classical Conditioning

Repeated associations between allegedly neutral stimuli and an active drug (unconditioned stimulus) can result in the neutral stimulus by itself eliciting a response characteristic of the unconditioned stimulus. Clinical treatment characteristics, such as white coats, the concurring hospital smell, the color, taste and shape of a pill can also act as conditioned stimuli and lead to a therapeutic response in patients, just because they have been paired with them in the past (Wikramasekera, 1985; Siegel, 2002; Ader 1997; Voudouris et al., 1990). Intriguingly, pharmacological conditioning followed by a placebo treatment administered in the same way as the drug used in conditioning, evokes very similar

physiological responses as the drug, both in humans (Goebel et al., 2002; 2005; 2009) and animals (Herrnstein, 1962; Ader, 1985; Siegel, 1985; McMillan, 1999)

1.3.2 Expectancy

In addition to conditioning expectations also play a central role in reinforcement learning of placebo responses to a specific psychosocial context. It has long been known that patients that were given a placebo expect future responses (Kirsch, 1985). Simple verbal cues have been used in experiments in order to modulate expectations of treatment outcome (Amanzio & Benedetti 1999; Benedetti et al., 1999). Thus, according to the strength of verbal suggestions, for instance, that it was a strong or weak analgesic, the very same placebo cream can actually cause a diverging intensity of analgesia in patients. (Price et al., 1999). Such verbal cues have been shown to mediate not only analgesic placebo effects, but led also led to changes in motor performance in Parkinson's disease (de la Fuente–Fernandez et al., 2001; Pollo et al., 2002), emotions (Petrovic et al., 2005) and brain responses in patients with drug addiction (Volkow et al., 2003). Moreover, expectancy was also shown to increase analgesic placebo response in presence of a conditioning protocol, implying that expectations can both evoke and modulate placebo responses (Amanzio et al., 1999; Voudouris et al., 1989; 1990) and also interact with other neurochemical systems, such as emotion and desire (Price et al., 2008; Vase et al., 2003).
The essential role of cognitive engagement to placebo responses is best shown in cases when it is missing, for instance in patients with Alzheimer's disease (AD), where cognition is crumbling. A loss of prefrontal control goes hand in hand with a loss of placebo responsiveness (Benedetti et al., 2006). Further studies confirmed this under the experimental setting of transient prefrontal opioid neurotransmission blocking with either pharmacological means (Eippert et al., 2009) or by repetitive trans-cranial magnetic stimulation (rTMS) (Krummenacher et al., 2010).

1.4 Biochemical pathways involved in placebo responses

There have been several biochemical pathways identified by which placebo responses can engage mechanisms of action in various somatic and cognitive systems.

The earliest and most striking placebo responses were found in studies on pain perception (Levine & Gordon 1984; Benedetti et al., 1995; Benedetti, 1996). Solely the expectancy of pain relief could lead to similar outcomes compared to treatment effects of analgesics. Furthermore, the efficacy of pharmacological pain treatment might also be modulated by conscious expectations of relief (Colloca et al., 2004). The corresponding neurobiological pathway for placebo analgesia is most probably the activation of endogenous opioids. Several studies could demonstrate a complete reversal of analgesic placebo responses by administration of the opioid antagonist naloxone (Levine, Gordon & Fields, 1978; Benedetti, 1996; Levine & Gordon, 1984), which supports the theory that endogenous opioids would be involved in some placebo responses (Fields & Levine, 1984). Further research has supported and extended these results by neuroimaging methods such as positron emission tomography (PET) (Zubieta et al., 2005; Wager et al., 2007) and functional magnetic resonance imaging (fMRI) (Wager et al., 2004; Kong et al., 2006; Price et al., 2007).
There has been a growing body of evidence suggesting that if a subject expects clinical or any other improvement after placebo administration, not only endogenous opioids, but also dopamine is released and effects, among other things, the mesolimbic dopaminergic system. In Parkinson's disease patients, for instance, administration of placebo led to dopamine increase in the striatum (de la Fuente-Fernandez et al., 2001; de la Fuente-Fernandez & Stoessl, 2002) and resulted in changes in firing of basal ganglia and thalamic neurons (Benedetti et al., 2009; Benedetti et al., 2004).

There are also indications of placebo treatment modulating the metabolic activity in brains of patients with depression (Mayberg et al, 2002) and expectations in patients with drug addiction (Volkow et al., 2003).

Hence, placebos mainly seem to affect the reward and motivation circuitry via a distributed dopamine and opioid network. Moreover, they also play a pivotal role in conditioning the immune and endocrine system.

1.5 Connections of placebo responses to autonomic nervous tone

Placebo treatment may also affect autonomic nervous system tone. Changes in cognition, such as emotions, are mostly reflected in modulations of the autonomic nervous system tone, which in turn can be measured by heart rate and heart rate variability (HRV). For instance, low HRV has been found to predict emotional stress (Nickel et al., 2003; Brosschot, 2007). Placebo treatment induced similar, naloxone reversible changes, such as respiratory depression (conditioned placebo side effect) (Benedetti et al., 1999), decreased heart rate and β-adrenergic activity (Pollo et al., 2003) and also caused symptomatic improvement in patients with hypertrophic cardiomyopathy after surgical implementation of inactive pacemakers (Linde et al., 1999). Along these lines, if negative emotions are changing HRV, placebo-induced expectations of enhancement might modulate autonomic nervous tone as well.

1.6 Research questions and aim of the study

Now, if placebo responses actually correspond to physiological changes through endogenous mechanisms, which are triggered by psychosocial stimuli in a therapeutical context, the placebo effect would thus rely on effective mobilization of the psychological reserve that can improve the state and function in the recipient. Since placebo depends on inherent physiological reserves, which means that placebo mechanisms are constitutively present in all individuals, does this imply that conscious expectation of performance increase might as well enhance the function in healthy populations, leading to potential ergogenic and nootropic effects? Placebo has been shown to affect physical performance in different populations and across different tests (Pollo et al., 2008; Wright et

al., 2009). However, little is known about placebo effects on mental test performance (Dawkins et al., 2011, Claguiri & Boakes, 2009). In addition, possible involvement of central and autonomic nervous system in responses to placebo under cognitive performance tests has not yet been elucidated.

Accordingly, asking questions about these interactions immediately evokes the following dilemma: How can cognitive and physiological mechanisms be effectively disentangled?

Building on the ideas of previous investigations on ergotropic placebo responses (Pollo et al., 2008), we seek to investigate this complex phenomenon by an enactive perspective, combining behavioral performance tests with physiological recordings and first person reports.

Consequently, the present study aims to explore if stimulating expectations of enhancement with a placebo intervention will lead to changes in behavioral (i.e. physical and mental performance) and electrophysiological indicators of cognitive, autonomic and muscular function.

Employing the three measures of this multi-layered process, one might be able to distinguish between subjective reporting bias, induced expectations and actual physiological changes within the participants.

Given this theoretical and empirical framework we want to test the following hypotheses:

1. Conscious expectation of a performance enhancing intervention will lead to measurable performance increases in healthy young subjects in tests of:

    1.1. voluntary maximal muscle contraction force
    1.2. voluntary muscle contraction repetitions (endurance)
    1.3. accuracy in attention and working memory tests, such as the oddball task.

2. Behavioral effects of enhancement expectation will be accompanied by measurable electrophysiological changes in:

    2.1. Amplitude and latency of event related EEG potential P3
    2.2. Myoelectrical activity of active muscles
    2.3. Autonomic nervous system tone

3. The subjective experience of performance will match with the behavioral measure and reflect a conscious expectation of performance increase.

2. Materials and methods

2.1 Participants

Upon approval of the study protocol by the State medical ethics committee, the study was conducted on 25 volunteers. Three participants were subsequently excluded due to missing data and for not adhering to the instructions. The participants were healthy, young students of the University of Ljubljana (mean age = 22 ± 2.4 years) of both genders (m/f = 9/12), who enlisted to participate in a study on Optimization of short cognitive and physical performance tests in healthy subjects employing inherent performance enhancement.

2.1 Experimental design and procedure

In agreement with the crossover study design subjects scheduled two test sessions to take place three to five days apart at the same time of day best suiting their sleep-wake pattern. An initial brief interview was done at the beginning of the first session to verify that participants respected the specified exclusion criteria (neurologic / psychiatric disorders, recent general anesthesia, smoking and absolute pitch) and requirements to abstain from strenuous physical exercise and alcohol, or depart from habitual (moderate) consumption of coffee and tea, or regular sleep pattern two days prior to the test session, and to familiarize them with the details of the study.

Participants were told that the aim of the study was to standardize brief tests of physical and cognitive performance in healthy population for later clinical use. To assess the full range of physiological test outcomes, tests would be performed at baseline and following a mild pharmacological manipulation. The latter entailed a natural stimulant (dubbed PEp, for performance-enhancing placebo), which was declared able to induce a measurable change in physical and cognitive performance in susceptible people. Such susceptibility would typically be accompanied by a mild calorigenic side effect. A control substance (labeled “C”) of the same flavor and appearance but devoid of stimulant effect would be

used for comparison in one of the two sessions. In fact, both potions comprised a vitamin C effervescent tablet dissolved in 2 dL of water. The study was deliberately not blinded to enable a full range of expectation-driven performance responses.

Participants were then seated in front of a computer screen presenting written instructions and relevant countdowns during the session. During the session the experimenter was taking notes, recording the behavioral performance data: leg extensions, maximal isometric force of handgrip and the detected target tone counts after every block of the three-stimulus oddball test. The following physiological electrophysiological signals were recorded during the session: electroencephalogram (EEG), electrocardiogram (ECG) and surface electromyogram (EMG) of the hand flexors of the dominant hand during the handgrip test.

2.2 Study design

The first experimental session started with individual calibrations of the performance test in order to standardize task difficulty (for details on the calibration cf. 2.3 below).

The next step was mounting of the EEG cap, and other recording electrodes, which were also connected to the EEG system M40 NicoletOne (CareFusion, San Diego, CA, USA).

The sequence of performance tests in the first run (Figure 1) was as follows: 3 instances of 15 second isometric maximal handgrip squeezes (HG), one minute of full leg extensions (LE) and six blocks of 3 minute auditory oddball test with silent counting (OB). The first run was followed by a brief intermission when participants watched the preparation of the stimulant or control potion and the experimenter waited to witness them drink it up. After additional 5 minutes "for optimal substance absorption", the second run started with OB in order to give the musculature enough time to rest for HG and LE. At the end of both sessions, another short interview investigated the subjective experience of the participants during both runs of the session, including feedback on the performance in the respective tests and intensity of a possible calorigenic side effect. At the

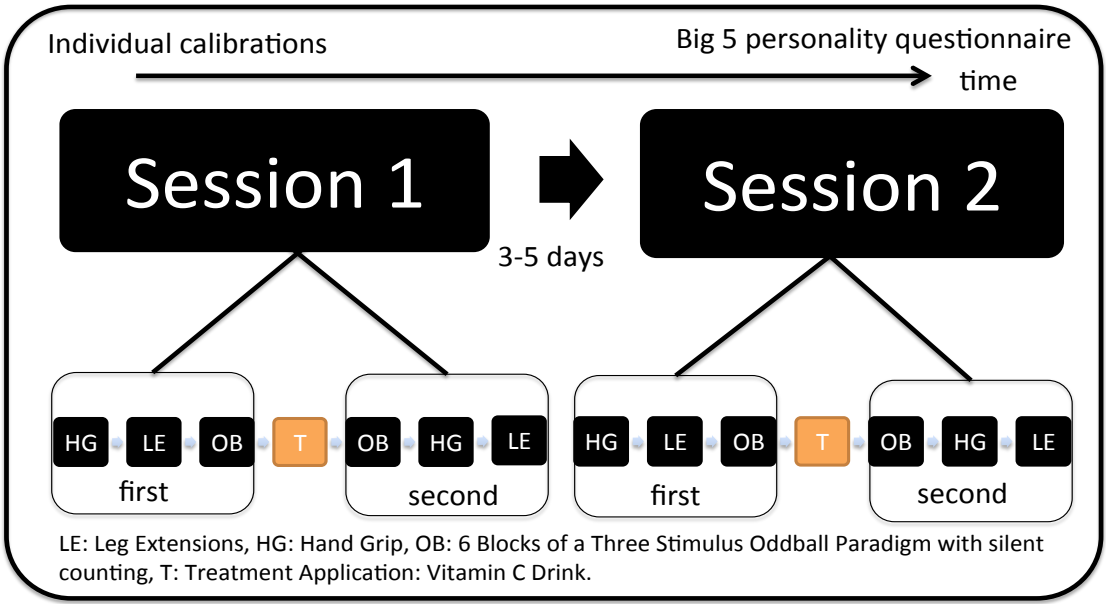

Figure 1. Experimental within-subject paradigm. All participants had to attend two consecutive sessions, each one starting with questions about adherence to standards and ending with a short interview on perceived performance. Individual calibrations (JND, 1RM) were performed only in the first session, whereas the personality questionnaire was filled out not until the end of the second session. The black boxes represent performance measurements; the orange boxes represent the time of vitamin C administration. A black frame shows first and second run of the same tests.

end of session two, a final 44-item personality questionnaire was answered to test for correlations between Big 5 personality traits (John et al., 1991, 2008) and placebo responsiveness.

2.3 Individual Calibrations

A standard fitness machine (Kettler Axos Fitmaster, Heinz Kettler GmbH & Co, Germany) was used for measuring leg extension workout (LE), which selectively involves the quadriceps muscles. The workout level was adjusted to individual ability as described earlier (Pollo et al., 2009). The maximum weight a subject was able to lift in a single extension was determined, starting at 15 kg and increasing the load by 5 kg steps until they could not lift the load. The last successfully lifted weight was recorded and multiplied by 0.6 for the load used in the subsequent muscle workout test runs.

Next was the individual just noticeable difference (JND) calibration. Analogous to the muscle workout test difficulty adjustment, the difficulty of the auditory oddball task was also individually calibrated. In short, individual subject's pitch differentiation detection threshold was established for difference in pitch from the 800Hz standard just noticeable difference (JND) using a staircase procedure. Two 50 ms long sinus tones were presented in sequence separated by x delay, and the participant had to decide if both tones were equal or different in pitch. The tones started with a standard tone frequency of 800 Hz and the second tone was incrementally increasing in frequency by 1 Hz. After every pair of tones, the participant indicated whether the tones were perceived to be of the same or different pitch by mouse clicks.

If the participant noticed the difference, the threshold was reached and the inverted staircase paradigm starting from a clearly perceptible difference, reducing the difference in pitch until the subject reported the second tone in a pair to be of the same pitch as the first. After the initial up and down sequence, the step size was reduced and the subject repeated three more up and down sequences. JND was computed as the mean difference from standard at reversal points for the last three up and down sequences. The calibrated oddball task was performed with a target tone frequency of 800 + 1.6*JND.

2.4 Performance tests

2.4.1 Leg extensions

Leg extensions (LE) were performed on a Kettler Standard fitness machine (Kettler Axos Fitmaster, Heinz Kettler GmbH & Co, Germany), which selectively involves the quadriceps muscles. The task was to do as many LE in one-minute time with legs stretching out completely. This task selectively measures the performance of both quadriceps muscles in terms of workload and endurance.

2.4.2 Handgrip

The measurement device was a Patterson Medical Jamar hydraulic hand dynamometer (cat# 5030J1). This test measured the maximum isometric force of the dominant hand flexor musculature. The subjects were instructed to follow the cues on the computer screen telling them when to squeeze the dynamometer with maximal. They repeated the test three times, squeezing for 5 sec and relaxing for 10 sec between trials, when the experimenters recorded the measured force from the dynamometer display. The mean of three consecutive measurements was used in subsequent analysis.

2.4.3 Auditory three stimuli oddball test with silent counting

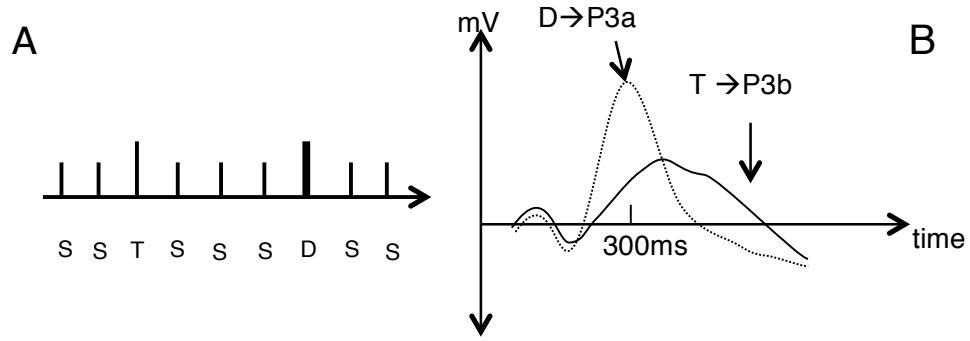

Figure 2. A: Scheme of the oddball silent counting (OB) paradigm and B: stimulus effects on measured event related potentials (ERP) obtained by surface electroencephalogram (EEG). Note that the different stimuli, distractor (D) and target (S), evoked by D and T, respectively, differ in maximal amplitude and latency.

Silent counting was used as a measure of target tone detection accuracy in the auditory three-stimulus oddball paradigm (cf. fig. 2). The oddball test consisted of 6 blocks of alternating easy and hard tasks. In each block 84 tones were presented with inter-stimulus interval of 2 s in pseudo-random sequence. The three stimuli were:

- A standard tone (S), which was a sine wave at 800 Hz (66.6% of stimuli)
- A target tone (T, target; 16.6% of stimuli), also a sine wave, either at 900 Hz frequency in the easy task version or closer to the standard stimulus, individually calibrated as described in section 2.3 in the hard task
- A compelling distractor (D: 16.6%), a white noise

The proportion of T and D was changed slightly in each block with the number of T ranging between 13 and 16 per block. The task of the participant was to silently count the number of targets presented and report the number at the end of each block, engaging attention and memory related processes. These processes can be assessed with brain activity recording methods such as EEG, where the stimuli of certain characteristics elicit specific event related potentials (ERPs), which were measured from 150 until 600 ms after stimulus presentation. The ERPs should be constant if the experiment is reproduced with the same conditions. On the right side of fig. 2, the typical ERP of standard stimulus is shown by the slim black line, D usually evokes potentials similar the dotted more early P3a component (measured from 150-400 ms post stimulus) and the T (target) component is shown by the P3b component (measured from 150-600 ms post stimulus) in bold.

2.5 Measures of Subjective Experience

At the end of each session, participants reported their assessment of own test performance (subjective experience), in ordinal numbers from 1 to 10. The participants reported their subjective experience of LE, HG, OB and their motivation both for before and after the treatment, when also feedback about any calori-

genic side effect was given.

2.6 Personality inventory data

The personality scores for Extraversion, Agreeableness, Conscientiousness, Neuroticism and Openness were obtained by a 44-item BFI questionnaire (John et al., 1991, 2008) at the end of the second session (cf. appendix 7.2 for exemplary BFI questionnaire).

2.7 Electrophysiological data

During the performance task runs ECG and EMG were recorded in order to detect changes in electrical brain response, heart and myoelectric activity. For measurement, a clinical 41-channel EEG setup was used and EEG activity was recorded at 36 electrode sites (Fp1/Fp2, F3/F4, F7/F8, FC1/FC2, FC5/FC6, C1/C2, C3/C4, CP1/CP2, CP5/CP6, T7/T8, TP9/TP10, P3/P4, P7/P8, PO3/PO4, O1/O2, Fz, Cz, CPz, Pz, POz, Oz) based on a 10-20 system using Ag/AgCl electrodes mounted on an elastic cap with reference at FCz and ground at AFz. To enable concurrent recording of electrooculogram (EOG) additional electrodes were placed below the left and right eye using the same reference. The signal was band passed and digitized with 16 bit precision and a resolution of 0.1526 μV. Sampling rate was set at 256 Hz using M40 NicoletOne EEG (CareFusion, San Diego, CA, USA). To enable later analysis, time of stimulus presentation was recorded on a separate channel along the EEG.
Two electrodes were used for EMG measurements on the forearm with the dominant hand and one electrode was used to measure ECG (for more detail, cf. Figure 4). Impedance was always kept below 10 Ohm and in most cases below 5 Ohm.

2.8 Data pre-processing and statistical analysis

2.8.1 Behavioral data

For each participant in both sessions, the placebo effect in LE, HG and OB was calculated. As the key effect of interest for all the behavioral methods was the modulation by session, a single value vas computed for each of the participants using the formula:

$$p_e = (e_{2P} - e_{1P}) - (e_{2C} - e_{1C}) \quad [1]$$

where p_e is the placebo effect of interest, e is the estimate of the parameter of interest (e.g. LE number, HG force and perceived performance), subscripts p and c denote placebo and control session, respectively, and subscripts 1 and 2 indicate the first and second run of a session, before and after treatment, respectively.

To test for statistical significance, a one-tailed t-test between placebo and control session was computed across all the participants for each of the behavioral measures. To determine the effect size, if applicable, Cohen's d (Cohen, J., 1988) was calculated for t-test results. The same procedure was applied to the data of subjective experience. The BFI personality questionnaire was evaluated according to instructions given by John and coworkers (1991, 2008) and the individual personality scores obtained were correlated to the effect size of the placebo response in legs and hands.

For OB silent counting performance, the accuracy was calculated as follows:

The measure of OB performance was percent accuracy (OBacc).

First, we calculated for each run the three block average mismatch (AM) between the presented (P) and reported (R) targets expressed as percent of P targets of equal task difficulty:

$$AM = \frac{\sum_{j=3} R_j}{\sum_{j=3} P_j} \quad [2]$$

Where j is oddball blocks of equal difficulty before and after treatment (3 blocks for each difficulty and each run: 12 blocks per session).

Second, if the participants counted less or exactly the number of targets, the AM measure was inversed in order to reflect average error (err). If the subjects counted to many targets, AM yielded figures bigger than 1. Therefore, we had to adjust the error measure accordingly (cf. fig. 3). In order to get two-digit percent, in both cases AM values were multiplied by 100.

$$R \leq P: err = (AM - 1) * 100$$

$$R > P: err = (AM - 1) * 100 \quad [3]$$

For better comparability to other behavioral performance measures, error was inversed to accuracy (acc) by subtraction from 1:

$$acc = 1 - err \quad [4]$$

The next step was subtraction of accuracy values in order to get within session differences (WSD):

$$WSD(OBAcc) = acc_2 - acc_1 \quad [5]$$

After obtaining WSD, the session difference was calculated analogous to the procedure in formula 1 as the following:

$$p_e = WSD_P - WSD_C \quad [6]$$

where pe is the placebo effect of interest, WSDp is the within placebo session

estimate and WSD_C is the corresponding estimate for control session.

To assess the effect of placebo on error differences between runs a three way mixed design Analysis of Variance (ANOVA) was performed with the within-subject factors *session* (placebo vs. control), *run* (first (pretreatment) vs. second (post-treatment)), and *oddball task* (easy vs. hard OB). We also tested for significant differences in target count dispersion between runs at both sessions (placebo and control) using Pitman t-test for variances of correlated samples. LE, HG and OB accuracy confidence intervals were calculated according to Morey, 2008.

Similar to the placebo effect calculation in the performance tests (cf. formulas 1 and 2), a measure for changes in subjective experience (SE) was obtained by subtracting SE session differences of control from placebo session:

$$SE_e = (SE_{2P} - SE_{1P}) - (SE_{2C} - SE_{1C}) \quad [7]$$

2.8.2 Electrophysiological data

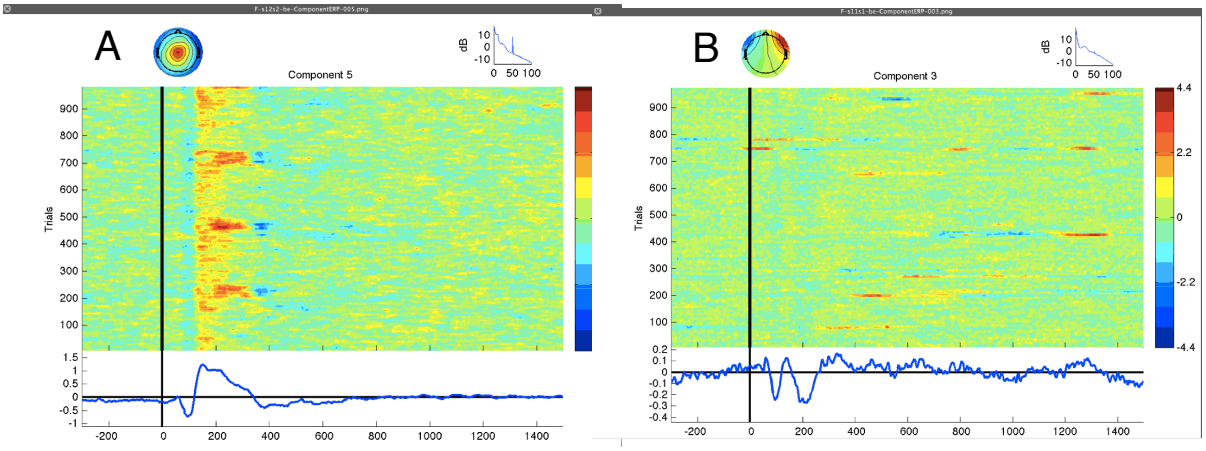

Figure 3. Individual Component (IC) plots for manual exclusion procedure. Note that plot A shows a distinct ERP structure across all trials and differs in specific subcategories (session, run, task, channel location). The power plot in the upper right does show a good frequency distribution within the signal, with some noise at 50 Hz from other electrical devices in the laboratory. Also the signal topography plot in the upper left seems to match with P3a and P3b topography (cf. fig. 4 for more details) All these criteria imply that this epoch captures important, task relevant neural activity and should not be excluded. In contrast to A, plot B shows mostly undesirable indications and would be most probably excluded. First off, there is no structure within single trials, neither in the grand average below. The power spectrum has an acceptable shape, however, the topology indicates that the main source of activity in this component seems to origin from occipital movements, not neural activity

For EEG, ECG and EMG data preprocessing and statistical analysis were adjusted according to their respective properties.

2.8.2.1 Event related potentials (ERP) analysis

The procedure described here was executed with a customized gCleanEEG Matlab script on the data of every participant, as follows: First, the EEG data was filtered with a high pass filter of 0.5 Hz using a second order IIR Butterworth filter. Second, the quality of data in each EEG channel was checked and channels with excessive noise were rejected and later interpolated, the signal was re-referenced to the average of all channels which showed a good signal to noise ratio (SNR). The next step was the creation of epochs (sequences of data from 300 ms before the tone onset, ending 1.5 s later, baseline across the whole epoch was removed from each channel) from the continuous EEG data. Then these epochs were sorted into bins, in total 24 specific categories: 2 sessions * 2 runs * 2 tasks * 3 stimuli. Fourth was the exclusion of bad epochs using several statistical parameters such as standard deviation, variance and root

mean square of amplitude difference between all time points in the respective epoch. The epochs differing more than 2.5 standard deviations from the mean were excluded from further analysis. Next step in EEG preprocessing was the signal decomposition into a set of independent components (IC) using the AMICA algorithm (Palmer et al., 2011). The rejection of IC cannot be automatized, therefore it was done manually, using a graphical plot (cf. fig. 3) and the following exclusion criteria: low SNR, strong correlation with EOG channels, high alpha frequency band amplitude, no visible structure of trials in the plot.

After epoch and IC exclusion, previously removed channels were interpolated and re-referencing to electrodes T9 / T10 (electrodes near to the ears) signal was done in accordance with previous studies (Polich, 2007). A mean of virtual sum channels was computed in order to have a measure for average activity in P3a (distractor) and P3b (target) topographical regions (Figure 4), with the selected channels being:

Target: CPz, CP1, CP2, Pz, P3, P4, POz, PO3, PO4
Distractor: FCz, FC1, FC2, Cz, C1, C2, CPz, CP1, CP2

Differences from standard were computed by subtraction of mean amplitude values of the corresponding standard epochs in the control and placebo treatment sessions. For visualization, the grand averages were low-pass filtered at 60 Hz. However, raw data were used for statistical analysis.

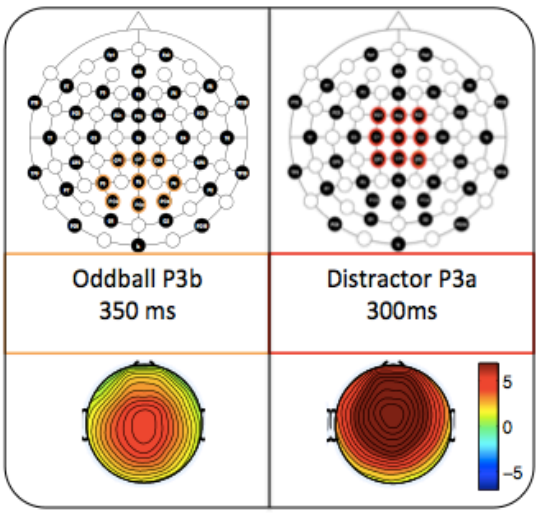

Figure 4. Topographies of Electrodes and Neural Activity. The top plots show the head scheme with all applied EEG electrodes. The lower plots show a typical ERP pattern upon target and distractor stimulation during intervals of maximal signal amplitude. The regions of highest target and distractor activity are marked in orange and red, respectively. These marked electrodes were selected to achieve best measure and representation of neural response upon target and distractor stimulation (average scalp voltage amplitude across respectively marked electrodes).

For each subject a mean time-course was computed for each of the sessions (a combination of stimulus type, task difficulty, run and session). P3a and P3b amplitudes were estimated as the mean signal value between 150 and 400 ms after presentation of the distractor, and between 150 and 600 ms after presentation of the target tone, respectively. Fractional latency of the two waves was computed as the time point at which the area under the (positive) signal reached 50% of the area during the respective time windows. As in a number of subjects the signal during the P3b window did not exceed the pre-stimulus baseline, the amplitude of difference from the standard was used instead for P3b fractional latency calculation.

To test for significant differences of mean amplitude and fractional latency between runs under placebo vs. control session, a mixed design ANOVA with the within subject factors *session* (placebo vs. control), *run* (first (pretreatment) vs. second (post-treatment)), *channel* (Fz, FCz, Cz, CPz and Pz), and *oddball task* (easy vs. hard OB) was performed in R.

2.8.2.2 Electrocardiogram (ECG) analysis

To obtain ECG signal an electrode was placed on the dorsum of the left hand using the same reference as the EEG channels and recorded on a separate channel along the EEG signal.

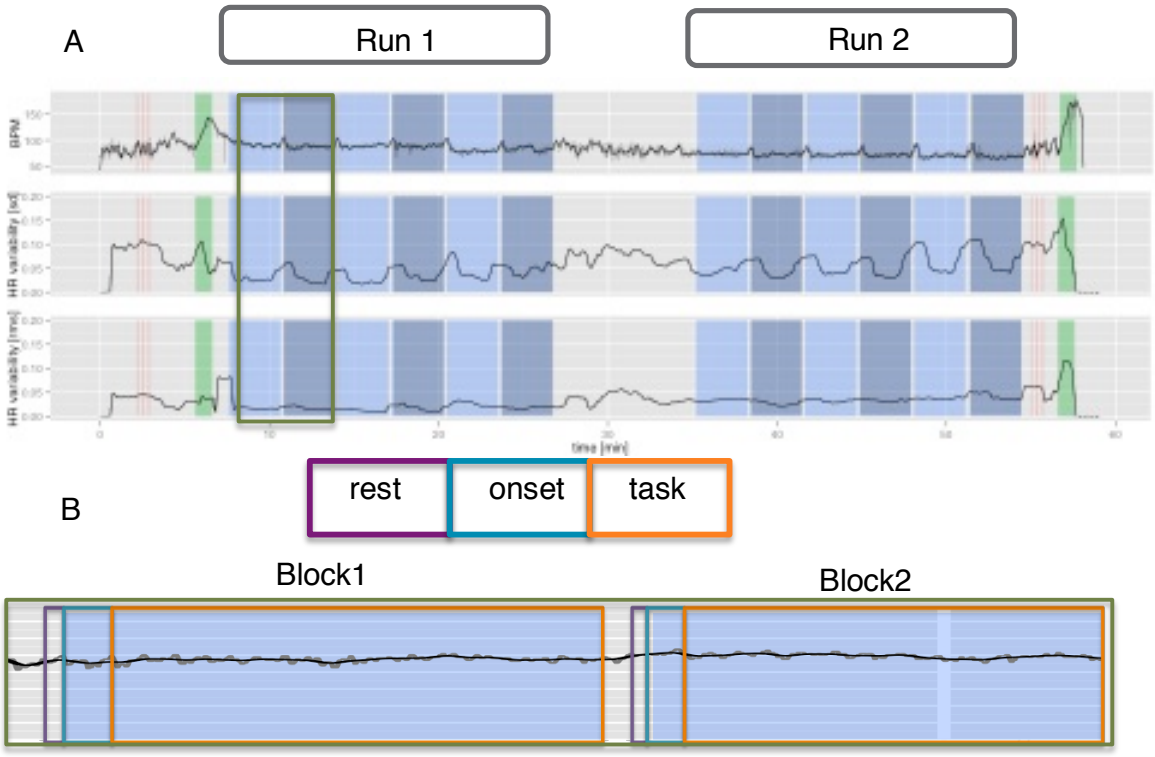

Figure 5. A: An exemplary full session recording ECG dataset. There were a total of 12 OB task blocks in each session, highlighted in blue. Only in these blocks, ECG data was preprocessed and analyzed. A green rectangle marks a snippet of ECG data between 14 and 20 minutes, containing the first complete and more than half of the second OB block. The same snippet has been enlarged in fig. B in order to visualize the different period classification of each block. The green rectangle denotes the snippet section, violet, turquoise and orange represent rest, onset and task period classes, which have been evaluated separately in order to account for different mental and physiological states the participants may have been in.

To identify the R peaks of the ECG, the signal was band-pass filtered between 8 and 20 Hz using rank 8 IIR Butterworth filter, a running maximum across a span of 1.2 s was computed and the signal was normalized to it. R peaks were defined as the point of local maxima of signal exceeding 3 standard deviations from the mean across the recording. Any peak that followed less than 0.3 s after the previous was automatically rejected, and periods when the R-to-R delay was less than 0.7 and more than 1.5 of the mean of the previous 5 were marked as suspect. The signal and peak estimates were manually inspected, missed or misidentified, peaks were corrected and periods of excessive noise were ig-

nored during analysis.

Once R peaks were identified, continuous heart rate (HR) was computed as 60 divided by R-to-R delay (in s), and the resulting beats per minute (BPM) value was assigned to the time period between the two peaks. Heart rate variability (HRV) was expressed first, as standard deviation in R-to-R peak delay across the period of interest, and second, as root of the mean squared difference (RMSD) between R-to-R peaks within a period of interest.
To inspect the individual time course, continuous HR and HRV were plotted as a function of time. Continuous HRV was computed using a sliding window in which HRV across 25 contiguous R-to-R delays was computed and the result assigned to the time interval between the middle R-to-R delay.
For the purpose of the statistical analysis, three intervals of interest were defined (Figure 5): *rest* - a 15 s window before the start of each block of the oddball task, *onset* - a 30 s window from the start of each block of the oddball task, and *task* - the time period from 30 s into the task until the end of the task (2.3 min). HR for each of the intervals of interest was computed as the mean of the continuous HR within the specified time window, whereas HRV was computed across all valid R-to-R intervals within each specified time window. The effects of time period, run and session on HR and HRV measures were assessed using repeated measures ANOVA.

Figure 5 shows an individual example on how HR and HRV were changing during different stages in one session of the experiment. As three periods (rest, onset and task) in each of six oddball blocks per run present a substantial number of repeated measurements on the same participant, Mauchly test for sphericity was used to check for asymmetries in the dataset and Greenhouse-Geisser significance correction was used to compensate for these sphericity violations.

In order to test for significant effect of session on differences in HR and HRV between runs, a mixed design ANOVA with the within subject factors *session* (control vs. placebo), *run* (first vs. second), *task* (easy vs. hard), and *period*

(rest, onset and task) was performed in R.

2.8.2.3 Electromyogram (EMG) analysis

Two electrodes were placed 2 cm apart from each other, 20 cm proximally to the wrist on the flexor aspect of the dominant forearm; the upper electrode on the arm was used as a reference, against which the other electrode was measured (Konrad, 2005)

A number of indices of EMG activity were computed from the acquired EMG signal. Before the analysis, the raw EMG signal was high-pass filtered at 10 Hz using rank 2 IIR Butterworth filter to remove slow-frequency drift in the signal. The resulting EMG signal was used to conduct zero-crossing analysis. In addition, the signal was converted to absolute values only, the upper envelope was computed and high frequency noise was removed using low-pass rank 2 IIR Butterworth filter at 8 Hz. The signal was then epoched between -1 to +9 s from start signal for each hand squeeze. To estimate the onset and offset of EMG activity, baseline signal variability was computed across 0.7s window before each start signal. Onset was defined as the first time point at which the value of the envelope exceeded 3 SD of the baseline for at least 0.6 s, and offset as the last time point at which the preceding 0.6 s of the envelope exceeded 3 SD of the baseline. To take into account the variability in overall signal amplitude due to differences in electrode placement, the epoched signal within each session was normalized to the value of the 75th percentile of the sorted samples within the session.

Based on the onset and offset estimate the following parameters were computed across the activity period for each trial: maximum amplitude (m_a), median amplitude (me_a), power (pw_a; sum of squared amplitudes), and number of zero-crossings (zc_a). To assess the effect of experimental manipulation on EMG parameters, a repeated measures ANOVA with the factors session, run, task and period was computed across the mean of three trials for each run.

All the listed preprocessing and analysis steps were conducted in Matlab (The Mathworks, Natick, 522 Massachusetts) using EEGLAB v10 (Delorme & Makeig, 2004), ERPLAB v2 (erpinfo.org) and adjusted FASTER (Nolan, Whelan & Reilly) packages. The statistical analyses were performed in R (R development core Team, 2012) and the results visualized using ggplot2 library (Wickham, 2009) and custom code.

2.8.3 Correlations

For determining correlations, Pearson's correlation coefficient r was calculated, and values were tested for statistical significance via the online calculator from varstats.net (http://vassarstats.net/textbook/ch4apx.html, © Richard Lowry, 2000-2013)

3. Results

15 out of 25 participants chose to start with placebo; therefore the order of sessions was roughly counterbalanced. However, after exclusion of 4 participants the ratio changed to 2:1; 14 of 21 participants chose to start with placebo.

3.1 Behavioral data

3.1.1 Performance Tests

Performance test results can be seen in figures 6 and 7**.** Figure 6 (A) shows that the average number of repetitions of leg extensions (LE) before treatment is higher in the control session. However, after treatment, in the control session there is a decrease of leg extension, whereas in the placebo session the same participants show an average increase in LE performance. In fig. 6 (B) indicates

no placebo effects on the handgrip (HG) performance test.

A paired-samples t-test indicates that performance after placebo treatment is significantly higher only in LE (M= 33.0, SD = 3.14, t(20) = 3,326, p = 0.002, *d* = 1.20) but not in HG (M= 30.7, SD = 2.72, t(20) = 1.107, p = 0.141, *d* = 0.48).
The oddball counting accuracy results shown in fig. 7 A, illustrate a difference in average accuracy between hard (calibrated) and easy (standard) version of the oddball counting task.

A three way Analysis of Variance showed a main effect of task (F(1,20) = 5.128, p = 0.035), yet neither session (F(1,20)= 0.0156, p= 0.90) nor run (F(1,20)= 3.90, p = 0.063) are significant factors, nor any interactions (all p > 0.06).

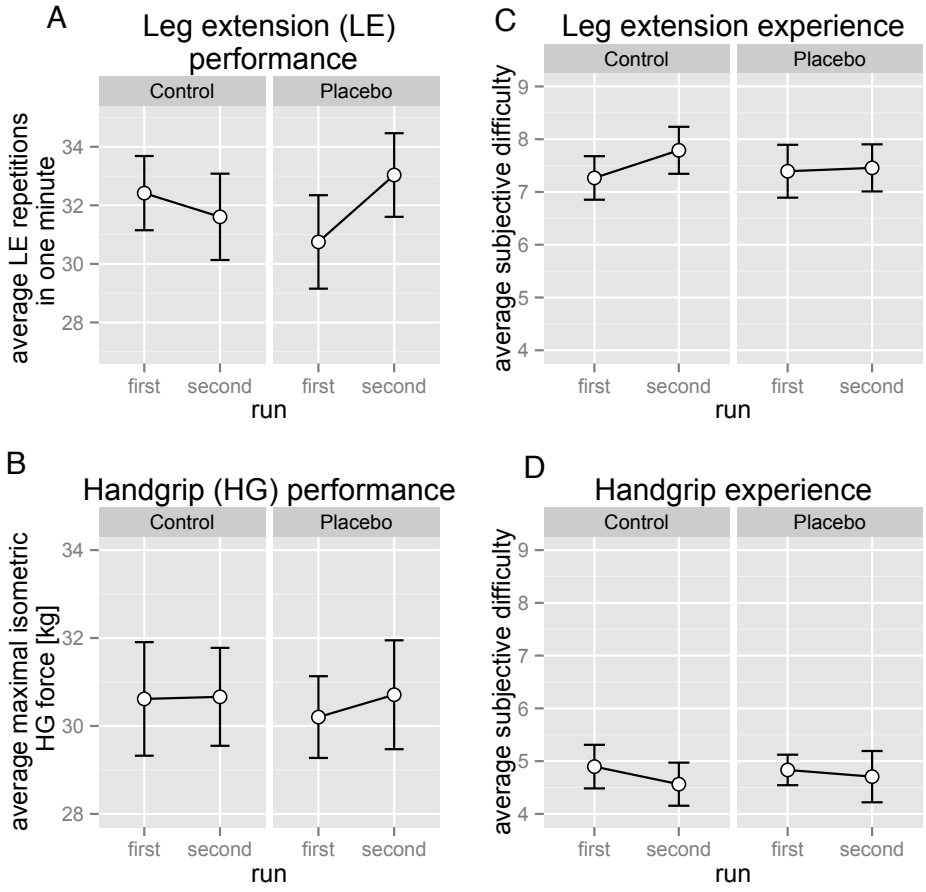

Figure 6. Average performance in leg extension (A) and handgrip test (B) and average perceived difficulty of the tasks (C and D, respectively) before and after treatment (first and second run, respectively) in both sessions. Points are showing the mean across subjects; vertical lines the 95% confidence intervals of normalized data

A Pitman-Morgan test of variance (table 1) for correlated populations indicated no significant difference in oddball average mismatch (AM) before and after treatment, neither in the control, nor in the placebo session (all $p > 0.07$)

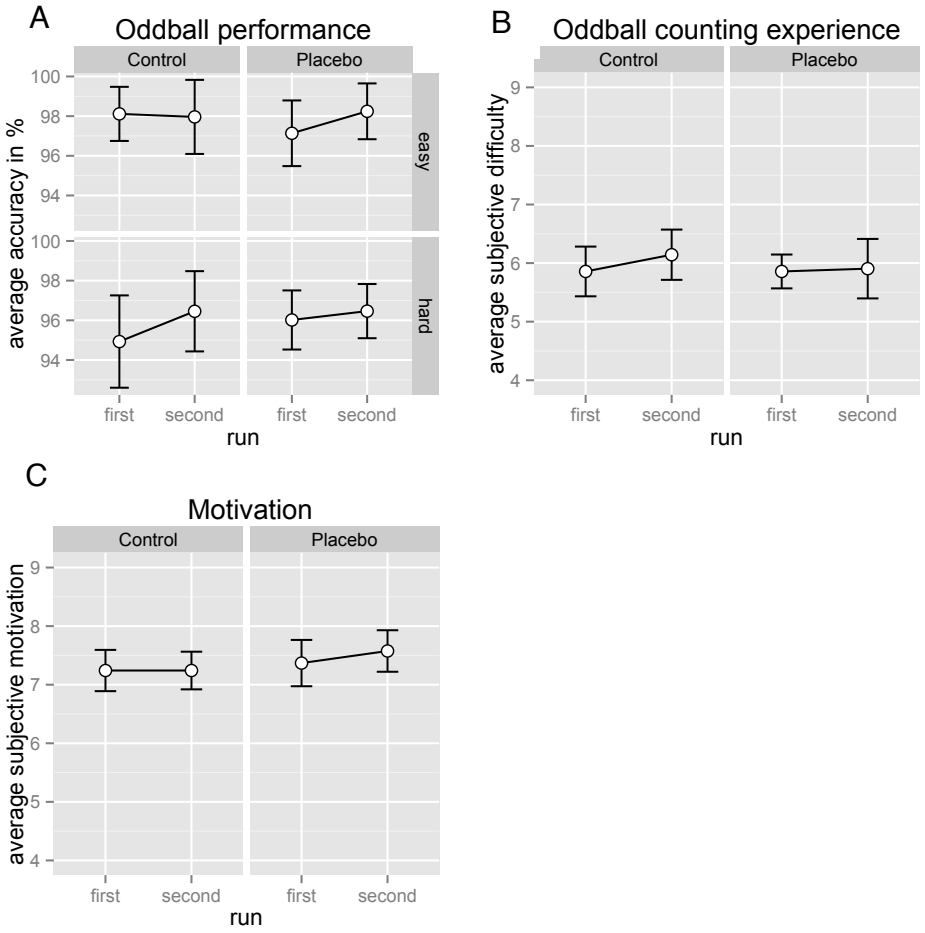

Figure 7. Average oddball accuracy (A) and perceived oddball task difficulty (B) and motivation (C) before and after treatment (first and second run, respectively) in both sessions and task difficulties. Points are showing the mean across subjects; vertical lines the 95% confidence intervals of normalized data.

Pitman-Morgan test of oddball AM variance between runs	
easy-control:	t(19) = 1.93; p = 0.068
easy-placebo:	t(19) = 1.90; p = 0.073
hard-control:	t(19) = 1.57; p = 0.133
hard-placebo:	t(19) = -0.41;p = 0.689

Table 1. Pitman-Morgan test for comparison of average mismatch (AM) variance of oddball (OB) blocks before and after treatment. Control and Placebo denotes the session, easy and hard denote the standard and calibrated oddball task, respectively.

3.1.2 Subjective experience

The results of perceived task difficulty concur with the behavioral data shown in figures 6 and 7. There were too little subjects to test if there was a significant change in subjective experience (SE) of calorigenic side effect intensity (SEI) after treatment in the placebo session, as SEI was only reported after treatment. Paired one-tailed t-test analysis suggests that there is no significant difference between treatment conditions in respect to perceived performance in HG ($t(19)=0.894$, $p= 0.191$, $d=0.343$), LE ($t(19)= 1.191$, $p= 0.124$, $d= 0.433$) and OB ($t(19)= 0.691$, $p = 0.249$, $d = 0.292$) performance tests, neither in subjective motivation ($t(19) = 1.045$, $p = 0.154$, $d = 0.416$).

There were significant correlations between behavioral measures and perceived performance within sessions, such as in control session between $SE_{C2\text{-}1}$ (HG) and $P_{C2\text{-}1}$ (HG) ($r(19) = 0.47$, $p = 0.016$) as well as between $P_{C2\text{-}1}$(HG) and $SE_{C2\text{-}1}$ of motivation ($r(19) = 0.45$, $p = 0.021$). All other correlations did not reach significance (all $p > 0.05$).

In the placebo session, there were significant correlations between $P_{P2\text{-}1}$(LE) and $SE_{P2\text{-}1}$(LE) ($r(19) = 0.38$, $p = 0.045$) and also between $P_{P2\text{-}1}$(LE) and SEI ($r(19)= 0.49$, $p = 0.012$). However, after calculation of the session difference $P_{P\text{-}C,}$ correlations between behavioral HG and LE performance difference (P_{HG}, P_{LE}) and subjectively perceived HG and LE experience difference ($PSE_{HG,}$ PSE_{LE}) did both not maintain significance. OB accuracy under easy and hard tasks, was correlated to SE_{OB} (all $r > 0.58$, $p < 0.004$) and to subjective motivation (SE_{MOT}) in the easy task ($r(19) = 0.55$, $p = 0.005$) (cf. table 2).

3.1.3 Personality inventory data

The BFI personality score Agreeableness was correlated to placebo effect in LE ($r(19) = 0.45$, $p = 0.021$) as well as Conscientiousness ($r(19) = 0.40$, $p = 0.036$). All other personality scores were not significantly correlated to any performance measure (all $r < \pm\ 0.36$, $p > 0.054$.)

3.1.4 Interaction of performance measures with control variables

Due to incomplete data, 3 more participants had to be excluded from OB performance measures in the hard task version ($n(OB\_hard) = 18$). Performance in the hard oddball task was correlated to average duration of sleep of participants: P_{OBacc}_hard*sleep ($r(16) = 0.62$, $p = 0.003$). The sequences of treatment conditions, meaning placebo in the first session and control in the second session or vice versa could be chosen by the participants in an unblinded manner. Even though participant's choice of treatment sequence was not exactly counter-balanced (seven of 21 started with the control session), treatment sequence of conditions was not significantly correlated to any of the performance measurements in control or placebo session (all $r < \pm\ 0.07$, $p > 0.38$).

3.2 Electrophysiological measures

3.2.1 Event related potentials (ERP)

As illustrated in Figure 8, the oddball task evoked the expected P3a and P3b event related potential (ERP) responses for distractor and target stimuli. Most notably is the distinct latency and amplitude difference between standard (black) distractor (red) and target (blue) evoked ERPs highlighting that these three different stimuli are represented in robust but unique patterns of neural

activation. For the distractor, the plots show lower P3a ERP amplitude before treatment compared to after treatment during the distractor time window (150-400 ms). The difference in amplitude appears across treatment sessions and OB tasks, being more pronounced in the easy than in the hard version of OB task.

The P3b amplitude peaks of target are about 150 ms later than those evoked by distractor independent of treatment, task and run. In the easy OB task version, there are very little differences in amplitude between run 1 and 2 in the control session, under placebo treatment, target evoked amplitude drops in central and posterior electrodes during a longer period of time (150-600ms), pronouncing P3b time window (400 – 600ms) and topography. Standard ERPs do not show any latency distinctions in these plots.

3.2.1.1 P3a and P3b amplitude

A four way within-subject analysis of variance with the factors channel (topography of the midline 5 electrodes: CPz, Cz, Fz, FCz and Pz), session (placebo vs. control treatment), run (first vs. second) and task (hard vs. easy version of oddball task) was computed in order to assess the effects of experimental sessions on the P3a and P3b components.

P3b amplitude

Figure 9 A displays line plots of oddball (target) stimuli mean amplitudes across topography, task difficulty and treatment conditions. Note that both differ in mean amplitude across single electrodes, as well as in specific sets of electrodes, which were selected at P3a and P3b (“Dist” and “Odd”, respectively) topography.

ANOVA revealed a significant main effect of topography ($F(6,126) = 103.29$, $p < 0.001$), reflecting higher P3b amplitudes in posterior regions, a main effect of

run ($F(1,21) = 9.4$, $p = 0.006$), reflecting an overall reduction in P3b amplitude after treatment intermission in the second run, a main effect of session ($F(1,21) = 5.34$, $p = 0.031$), reflecting P3b amplitude differences between treatment conditions and a session x run interaction ($F(1,21) = 5.56$, $p = 0.028$), reflecting a larger decrease in P3b amplitude in the placebo than in the control session.

To test whether the session x run interaction actually reflected an overall difference in ERP time course between the two sessions, ANOVA was also computed on mean amplitude in response to the standard stimulus in the same time window and found no significant effects, neither of run ($F(1,21) = 2.25$, $p = 0.149$), nor of session x run interaction ($F(1, 21) = 0.02$, $p = 0.886$).

P3a amplitude

As well as observed in target (P3b) mean amplitude, Figure 9 B displays line plots of P3a ERP amplitudes evoked by distractor stimuli (P3a). Four way analysis of variance indicated the following significant factors: channel ($F(6,126) = 31.46$, $p < 0.001$), reflecting the central topography of the P3a component, run ($F(1,21) = 23.18$, $p < 0.001$), reflecting a distinct reduction of P3a amplitude in both experimental sessions. ANOVA also yielded significant run – channel ($F(6,126) = 3.24$, $p = 0.005$) and task – channel ($F(6,126) = 6.26$, $p < 0.001$) interactions, however, in contrast to P3b, no significant session x run interaction ($F(1,21) = 2.51$, $p = 0.128$.

ERP grand averages

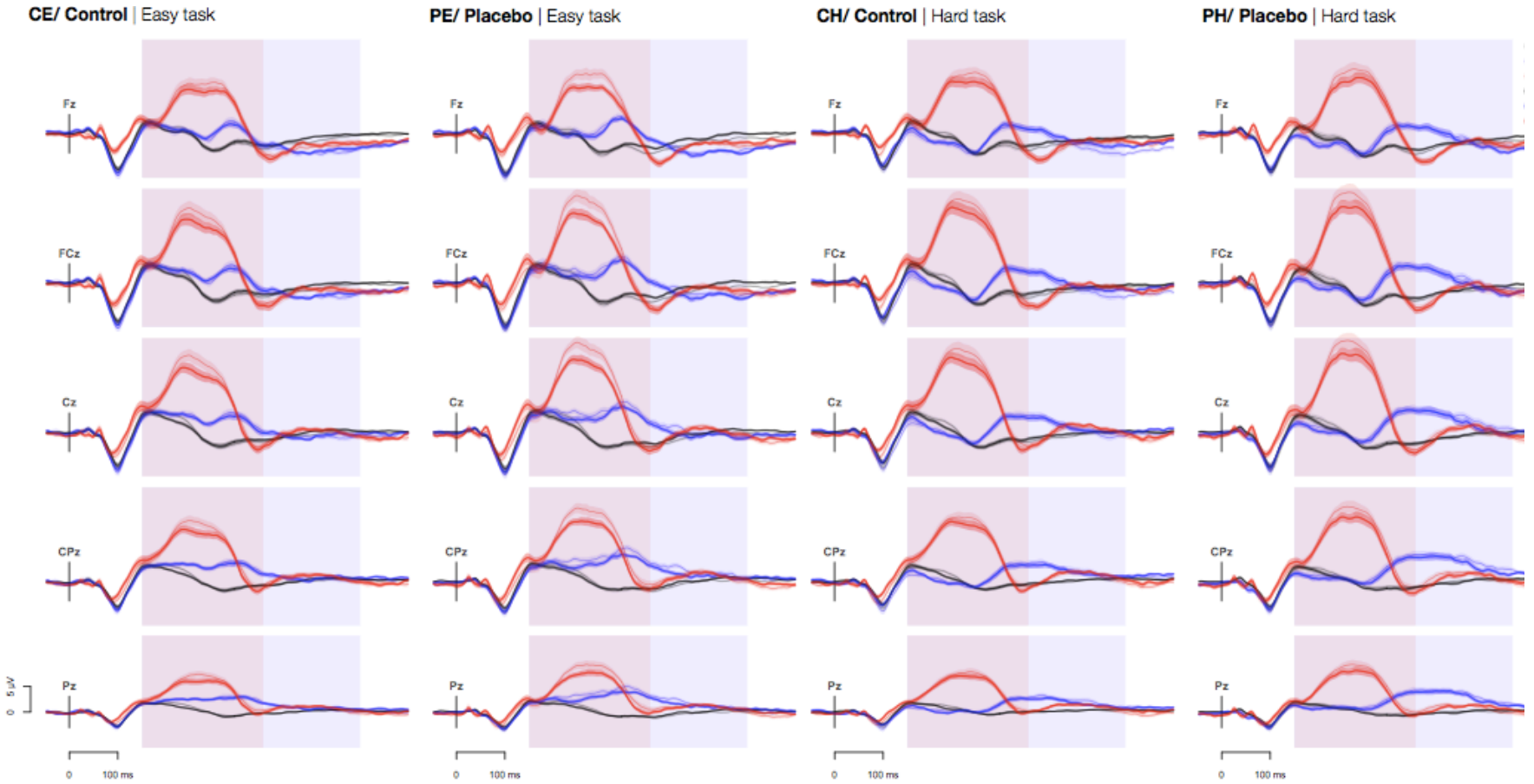

Figure 8. Grand averages of EEG ERPs evoked by standard, oddball and distractor stimuli in placebo and control session. Mean surface voltage of all participants (in μV) plotted against time (in ms) for the midline five channels (Fz, FCz, Cz, CPz, and Pz) (cf. fig. 4 for detailed reference). Time courses are shown separately for standard (black), target (blue) and distractor (red) stimuli, with time courses for the second run of a sessions shown in thicker lines compared to the first run and separately for each oddball task difficulty and treatment session: CE – easy task during control session, PE – easy task during control session, CH – hard task during control session, PH – hard task during placebo session. The color-shaded background highlights the time windows in which the mean amplitude of P3a and P3b was computed. Red: 150-400 ms denotes early components and distractor (P3a) window. Blue: 400-600 ms denotes late components and target (P3b) window.

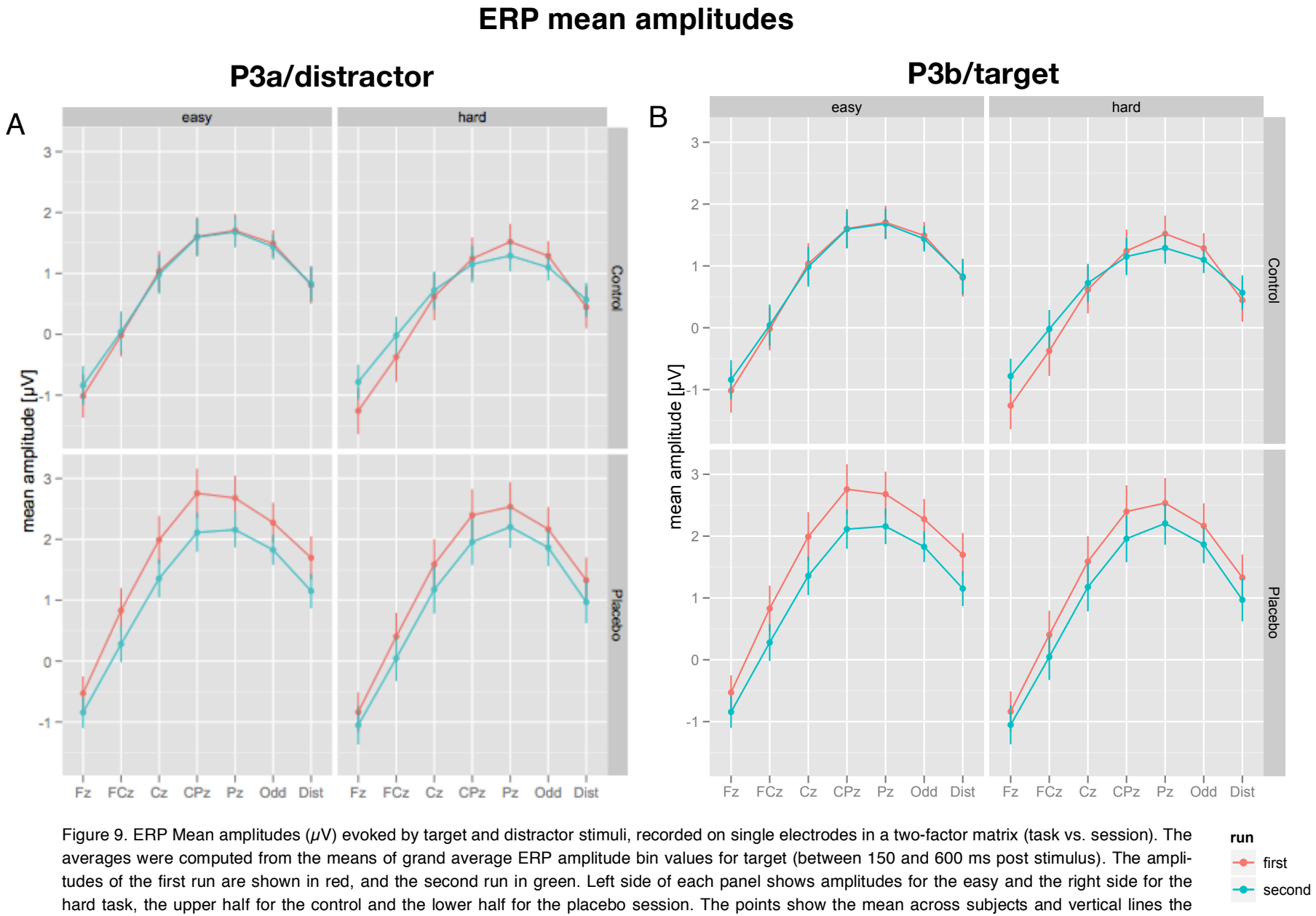

Figure 9. ERP Mean amplitudes (μV) evoked by target and distractor stimuli, recorded on single electrodes in a two-factor matrix (task vs. session). The averages were computed from the means of grand average ERP amplitude bin values for target (between 150 and 600 ms post stimulus). The amplitudes of the first run are shown in red, and the second run in green. Left side of each panel shows amplitudes for the easy and the right side for the hard task, the upper half for the control and the lower half for the placebo session. The points show the mean across subjects and vertical lines the standard error of the mean. The “Odd” and “Dist” electrodes represent a portfolio of electrodes of P3b and P3a topography (See fig. 4 for detailed reference).

Correlations to behavioral measures

We investigated whether the observed placebo effect on the P3b mean amplitude correlated with any of the behavioral performance measures. In order to achieve that, we first computed the placebo effect for the summary P3b mean amplitude over the 5 midline channels in the control session, the session difference between mean amplitude changes across the mean of the five midline electrodes (CPz, Cz, Fz, FCz and Pz) in the easy and hard version of the oddball task according to the procedure done for the behavioral measures (cf. formula 1) and then computed Pearson's r between P3b mean amplitude and all behavioral performance measures (HG, LE, OBacc) for the easy and hard version of the task. None of the correlations between summary P3b mean amplitude and behavioral performance placebo effect measures reached significance (all $r < 0.32$, $p > 0.098$). Looking only at the within session differences (run2 - run1) P3b mean amplitude was correlated to the behavioral OB accuracy effect $P_{P\text{-}C}(OB)$ in the easy version of the task ($r(19)= 0.48$, $p = 0.027$). However, no further significant correlations could be found, neither in the placebo treatment session, nor in the hard version of the oddball task (all $r < 0.35$, $p > 0.077$).

3.2.1.2 P3a and P3b fractional latencies

As described in the methods, the influence of experimental conditions on P3a and P3b latency was estimated based on summary signals representing average amplitude over those channels, which show most pronounced ERP response to the distractor and target stimuli. For reference, fig. 4 indicates the topographies of the selected electrode sets. A four way within-subject analysis of variance with the factors channel (topography of the midline 5 electrodes: CPz, Cz, Fz, FCz and Pz), session (placebo vs. control treatment) run (first vs. second) and task (hard vs. easy version of oddball task) was computed separately for distractor and target stimuli in order to assess the effects of experimental conditions on the P3a and P3b latency.

P3b fractional latency

Figure 10 A shows the fractional latency estimate of P3b (target) average amplitude peaks. ANOVA revealed a significant main effect of channel ($F(6,126) = 31.17$, $p < 0.001$) reflecting different ERP latencies in anterior and posterior electrode topographies, a significant main effect of task ($F(1,21)=126.17$, $p < 0.001$), reflecting longer latencies for hard compared to easy version of the oddball task, a significant main effect of run ($F(1,21)= 11,97$, $p = 0.002$), reflecting shorter latencies in the second run and a significant run x channel interaction ($F6,126) = 3.98$, $p = 0.001$) reflecting a stronger latency decrease in the second run in posterior compared to anterior regions.

P3a fractional latency

The P3a (distractor) latencies in fig. 10 B show a different pattern: ANOVA reveals that for P3a latency a significant main effect of run ($F(1,21) = 8.26$, $p = 0.009$), reflecting shorter latencies in the second run, a significant main effect of task ($F(1,21)= 15.58$, $p < 0.001$), reflecting shorter latencies in the hard compared to the easy task version and a significant main effect of channel ($F(6,126)= 8.00$, $p < 0.001$), reflecting shorter latencies in central compared to anterior and posterior topographies. Furthermore, one can observe a significant session x task interaction ($F(1,21) = 4.66$, $p = 0.042$), reflecting shorter ERP latencies in the hard task in the placebo session compared to control and a task x channel interaction ($F(6,126) = 9.84$, $p < 0.001$), reflecting shorter ERP latencies in the central regions in the hard task compared to the easy task.

P3a and P3b fractional latencies

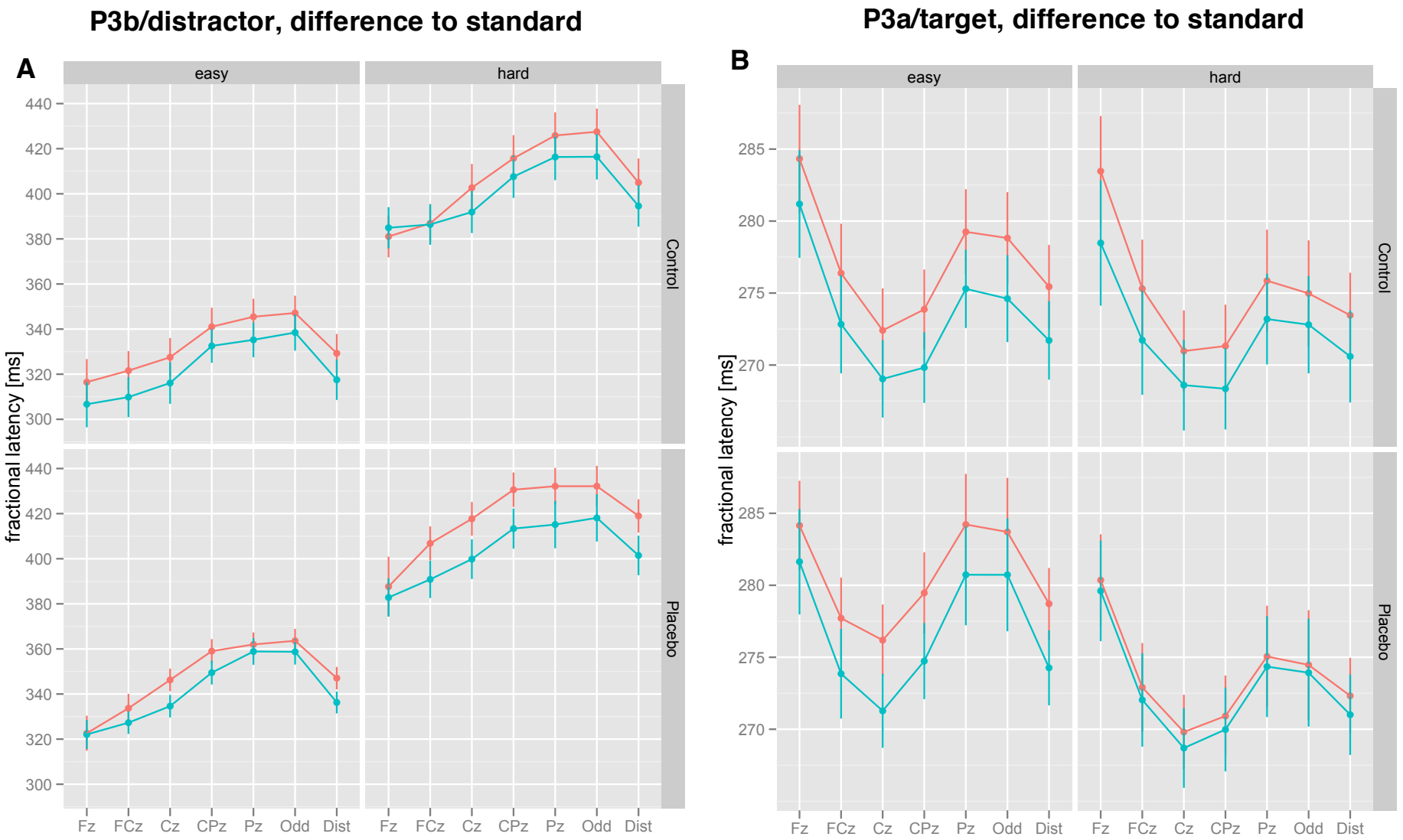

Figure 10. Fractional Latency (in ms) of P3b (target) and P3a (distractor) maximum amplitudes, with baseline (standard) latency subtraction plotted against electrode topography, treatment session, task difficulty and run. The points show the mean across subjects and vertical lines the standard error of the mean

3.2.2 Heart rate measures

In order to compute the influence of experimental sessions on autonomic nervous system tone, we measured heart rate (HR) and heart rate variability (HRV) and calculated a mixed design four way ANOVA with the within subject factors *session* (control vs. placebo), *run* (first vs. second), *task* (easy vs. hard) and *period* (rest, onset and task).

Figure 11 A shows the average heart rate in beats per minute in first and second run of all participants (before and after treatment, respectively) at different periods in both sessions. A four way repeated measures ANOVA indicated a significant main effect of period ($F(2,42) = 118.17$, $p < 0.001$), reflecting higher heart rate during rest, lower at onset and lowest during performance of the oddball task, a significant main effect of run ($F1,21) = 31.25$, $p < 0.001$), reflecting lower heart rate in the second run and a significant task x run interaction ($F(1,21) = 4.35$, $p = 0.005$), reflecting more reduction of HR during the second run for the easy task, which was most pronounced in the rest period. There was no significant modulation of HR due to session (all $p > 0.11$).

In Figure 11 B one can observe standard deviation (SD) of heart rate variability (HRV). A four way ANOVA revealed a significant main effect of period ($F(2,42) = 24.38$, $p = 0.014$), reflecting highest variability during task onset and lowest during task performance, a significant main effect of run ($F(1,21) = 33.08$, $p < 0.001$), reflecting an increase in HRV in the second run and the significant task x period ($F(2,42) = 9.67$, $p < 0.001$) and run x period ($F(2,42) = 15.07$, $p < 0.001$) interactions, reflecting higher HRV during task onset in hard task, as well as higher increases in HRV during onset in the second run. Again, there was no significant modulation of HR due to session (all $p > 0.09$).

Lastly, in fig. 11 C one can observe root mean square difference of HRV.
A four way ANOVA revealed the significant main effect of run ($F(1,21) = 18.40$, $p < 0.001$), reflecting a decrease of HRV in the second run. There was no sig-

nificant modulation by session (all $p > .45$).

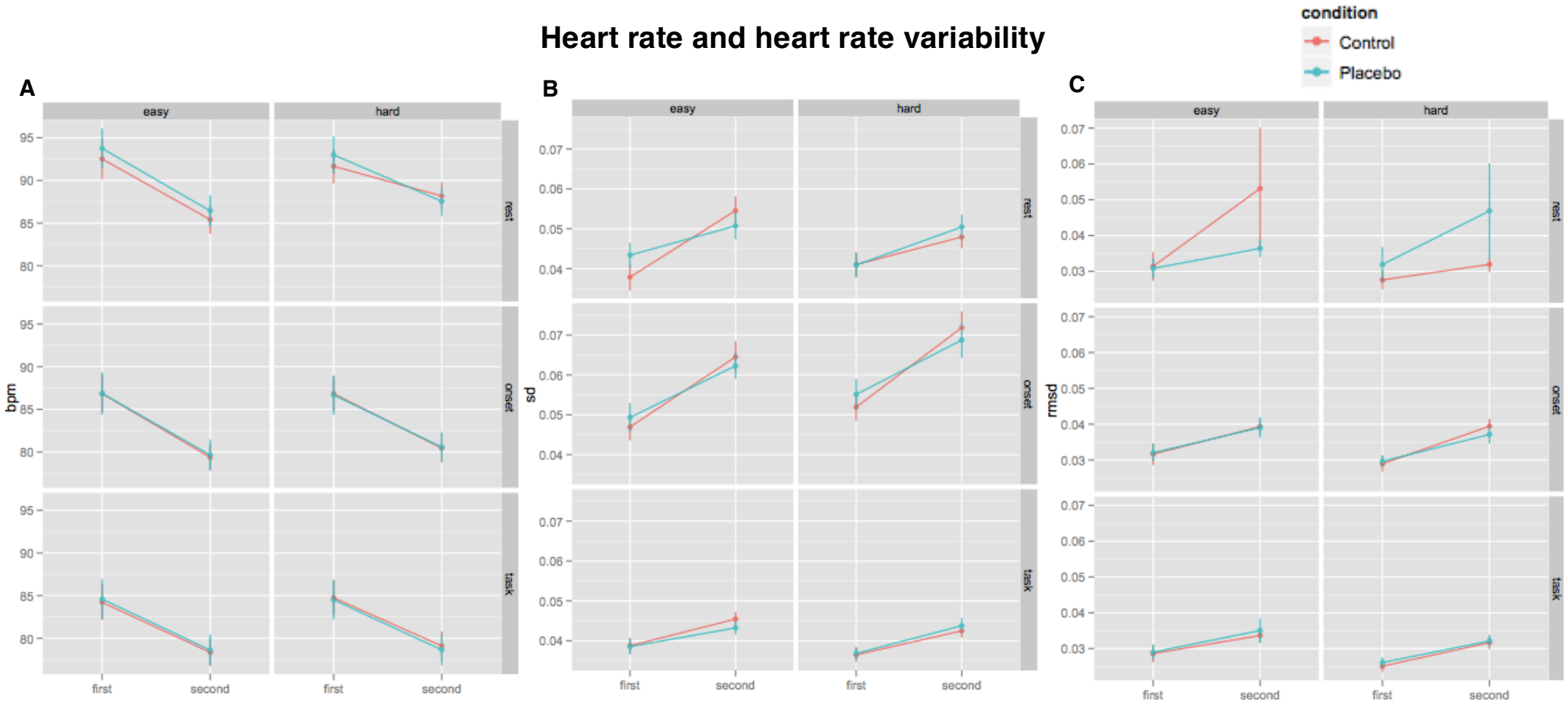

Figure 11. A: average heart rate (bpm), B: average heart rate variability (HRV) (standard deviation (SD) of bpm), and C: average heart rate variability (HRV) (root mean square (rms) of bpm) across participants during rest, onset and task periods. The points show the mean across subjects and vertical lines the standard error of the mean.

3.2.3 Electromyogram (EMG) measures

Possible effects of experimental sessions on EMG measures during the hand-grip performance test were assessed by a two-way within subject ANOVA with factors session (control vs. placebo) and run (first vs. second). None of the analyses indicated significant main effects or interactions for any of the EMG measures (all $p > 0.05$).

4. Discussion

4.1 Behavioral performance and subjective perception

The aim of the study was to test placebo as performance enhancing substance in both physical and cognitive terms. Starting out with the first hypothesis, that physical performance would be increased under placebo session, the results of the study show that the parameter influenced by ergogenic placebo was total muscle workout and not maximal isometric force.

In the leg extensions tests, there was a significant increase, which replicates the results of other studies on performance enhancement by placebo administration (Benedetti et al., 2007; Foad et al., 2008; Pollo et al., 2008). On the other hand, our results do not show performance differences in maximal handgrip force (HG). One explanation for the inhomogeneous outcome in the physical performance test might be that the nature of motor performance tasks is different. There is a stronger endurance aspect to one minute of LE than to 15 seconds of maximal handgrip with breaks in between. Given the speculations about the existence of a central governor of fatigue, constantly holding a physiological reserve capacity to provide protection against damage (Hampson et al., 2001; Lambert et al., 2005), the results of this study might suggest that if such a fatigue governor was affected by expectations of enhancement, the physiological reserves would be released more effectively during endurance tasks.

Additional support for comes from correlations between subjectively experienced performance increase and actual physical performance in LE, which was present only in the placebo session. This suggests a neurobiological coherence between subjective expectation and task performance.

The next hypothesis, that conscious expectation would also increase oddball silent counting (OB) accuracy could not be confirmed: Even though the silent oddball counting performance test applied in our study was aimed on auditory

working memory, one might be able to compare the performance outcome to the results from studies on visual working memory. False feedback was used to test effects of placebo on sustained attention (Colagiuri & Boakes, 2009), other studies tested for expectancy effects of caffeine consumption on Stroop task accuracy (Dawkins et al., 2011). Both methods have shown a significant performance increase due to placebo administration. In our study accuracy levels of sessions did not differ significantly from each other. There might be another possible interpretation of placebo not increasing accuracy, however leading to an increase in efficiency of cognitive resource allocation. This theory will be further elaborated on in the P3b mean amplitude discussion.

4.2 Electrophysiological measures

Our second main hypothesis stated that behavioral effects of expected enhancement would be accompanied by changes in the following electrophysiological measures: event related potential (ERP) P3 mean amplitude and latency, autonomic nervous system tone, electromyogram (EMG) surface amplitude.

4.2.1 ERP mean amplitude

P3b mean amplitude

First of all, significant decreases in P3b amplitudes during the oddball counting task in the second run of a session were found in the placebo session and not in the control session. According to Luck (2005) the P3 amplitude “is larger when subjects devote more effort to a task, leading to the proposal that P3 amplitude can be used as a measure of resource allocation“. Hence, the significant decrease of P3 ERP amplitude in the placebo session could therefore be either interpreted as a decrease in resource allocation or a decrease in attention and motivation. However, the results of subjective experience display that motivation increased under placebo administration. A logical inference would be that if motivation increases, P3 amplitude will increase as well as motivated subjects will

have spent more effort on the oddball counting task. However, the results showed the opposite: there was a decrease in P3 amplitude, but no decrease in motivation. Moreover, the behavioral OB performance was comparable in both sessions. Given the model of Luck (2005) and our subjective measures of motivation were correct, the ERP amplitude was actually expected to increase after the placebo. One possible explanation for the amplitude decrease, implying less resource allocation, could be that the processing capacity of calibrated and uncalibrated target stimuli was simply lower due to an expectation effect on cognitive performance. This effect would not reveal itself as an increase in the expected behavioral performance but as an increase in efficiency of neural resource management. Intriguingly, the measured nootropic effects are very similar to those found after caffeine treatment (Pan et al., 2000), which suggests that by placebo treatment, expectations of increased mental performance might have triggered conditioned caffeine responses. However, further research needs to be conducted in order to test this theory.

P3a mean amplitude

Results for P3a mean amplitude were as expected. Increased P3a amplitude in hard oddball task is consistent with the context updating theory of P3 in literature (Polich, 2007). Lower P3a amplitude in both sessions after treatment might be explainable by a learning effect, habituating to the infrequent appearance of the distractor (Rushby et al., 2005). Not only have P3a and P3b ERP components different functionalities in the context updating theory, they are also suggested to be driven by different neurotransmitter systems (Polich, 2007). This might explain the dissociation between P3a and P3b amplitude changes after placebo treatment. Interestingly, in this study P3b, the parietal/norepinephrine related component and not P3a, the component related to frontal/dopaminergic processing, seems to be the one more affected by placebo treatment. Given that most placebo responses have been associated with dopaminergic activity, this finding is surprising and suggests the possibility of a norepinephrine related placebo effect.

4.2.2 P3a and P3b latency

According to our next hypothesis that expectations of enhanced mental capacities would lead to improved mental performance, one might expect shorter P3a and P3b latencies under placebo session, due to a placebo response. However, this was not observed in this study. In other studies there have been indications of placebo-induced improvement in overall performance and increased attention and reaction time (Dawkins et al., 2011, Colagiuri & Boakes, 2010). If the OB task was comparable to a Stroop paradigm, one could say that the results are not surprising. It is well documented in EEG literature (Luck, 2005) that in hard tasks P3 latency is not always delayed, for instance, under the incongruent session of the Stroop task, as the P3 component reflects only one stage of many in signal processing. P3 and P3b latencies did however decrease after treatment in both sessions, probably as the immediate effect of training within every session.

4.2.3 Autonomic nervous system tone

Regarding the next hypothesis about expectation-induced modulations on sympathetic and parasympathetic nervous tone, ECG recordings displayed that there was no effect of treatment . In ECG however, run was clearly a factor. The effect observed might stem from a systematic decrease of heart rate (HR) and increase of heart rate variability (HRV) in the second run after each treatment, presumably due to participants settling down and physically relaxing with the end of the session approaching.

4.2.4 Electromyographical (EMG) activity

EMG measures of hand flexor muscles did not significantly differ in amplitude or frequency across treatment conditions. This coincides with behavioral and per-

ceived measures for handgrip performance. It seems that placebo treatment had no effect on electromyographical activity in the hand flexors, although this does not imply that the same holds for myoelectrical activity in quadriceps muscles during leg workout.

4.3 Placebo responsiveness: connections to genetics personality

Given the wide range of individual differences in placebo response magnitudes, a central issue in placebo research has been the search of specific characteristics predicting placebo responsiveness a priori to the treatment. Psychosocial, behavioral, personality and demographic variables have all been suggested to modulate susceptibility and indeed, they have been all found to play a certain role, yet were present only inconsistently across trials (Kaptchuk et al., 2008). Until now, a promising trace towards a predictor for placebo susceptibility might be genetic factors. At present there is one study suggesting that some genetic variants causing social anxiety disorder related to serotonin (Furmark et al., 2008) to be a positive predictor of susceptibility. On the other hand, a different study (Leuchter et al., 2009) suggested that major depression caused by polymorphisms in the protein monoamine oxidase successfully predicted a lower magnitude of placebo response. Social anxiety disorder and depression are usually associated with certain personality traits, such as elevated suggestibility. There are some indications that high suggestibility is a predictor to high placebo responsiveness (de Pascalis et al., 2002).

Moreover, other certain personality traits linked to strong dopaminergic neurotransmission, such as novelty seeking, behavioral drive and fun seeking have also been suggested to enhance placebo analgesic response (Schweinhardt et al., 2009), whereas harm avoidance and reward responsiveness did not. Interestingly, P3 amplitude seems to be correlated to the same character traits (Hansenne, 1999) and might therefore also be a good measure for dopaminergic neurotransmission, especially the P3a subcomponent (Polich, 2007).

This study reinforces the connection between placebo susceptibility and personality traits. The BFI traits Agreeableness and conscientiousness were both correlated to the performance increase in LE in the placebo condition, whereas the other three traits, including openness, were not effectively correlated. By now, in contrast to the temperament and character inventory used in previous mentioned studies, it is not clear how and which endogenous neurotransmitter activity might influence BFI character traits (Paunonen & Jackson, 2000). In order to find out if personality robustly predicts individual susceptibilities for placebo effectiveness one needs a bigger sample and a more extensive personality analysis.

4.4 Strengths and limitations of this study approach

A limitation of previous studies on placebo using a deceptive paradigm has been a possible overestimation of the detected effect size, due to putative unequal expectations of participants in treatment groups and of course, so does the unblinded design of this study as well (Kirsch & Weixel, 1998; Pollo et al., 2001, 2008; Vase et al., 2002). However, a clear strength of this particular study paradigm is that within subject measures can be compared to rule out much of possible confounding from unequal information and history artifacts.

For instance, even though vitamin C as an antioxidant has potential ergogenic features, nevertheless, in the second run of the control session, there was no significant performance increase in either of the tests applied, implying that in this study no ergogenic effects of vitamin C could have occurred. Furthermore, by the choice of healthy participants disease related confounding could be excluded as well. Therefore, only regression to the mean and reporting bias remain as possible sources of insecurity about the effects measured. Subjective reports and electrophysiological recordings constitute a good complementation to behavioral performance tests. In addition, the repeated measures design in

general represents a more sensitive measure and at the same time needs smaller samples for adequate statistical power.

Another limitation of the present study lies within the methods used for preprocessing of event related potentials (ERPs) from EEG recordings. Until now, the fact that there has been much controversy about a standardized way of ERP data analysis made many researchers use disparate protocols and methods. Signal to noise ratio is among the key issues in ERP analysis leading to a question of general trade-off: How much can and should the signal be purified without loosing too much essential information? The approach we took was as unbiased as possible using statistical exclusion criteria. However, when it comes to manual identification of the quality of individual components (IC) one cannot guarantee complete reproducibility of the process. Not even would the algorithm calculating the ICs provide the same results if run twice on the same dataset.

Furthermore, it can be argued that the ultimate meaning of the P3 components has certainly not been discovered yet. As a basic and very general link in the auditory and visual signal processing chain and according neural to the inhibition hypothesis (Polich, 2007) one can certainly assume that P3 amplitude and latency may reflect cognitive performance, however, this is surely not the only possible interpretation of the P3 component. In order to investigate which facets of cognition can be modulated by possible placebo responses upon expectation of cognitive performance increase in more detail, one might use more sophisticated tests in future studies, such as reaction time, the Sternberg memory test and the Conner's continuous performance test.

Concerning the EMG results, some authors generally would not recommend sampling rate below 1000 Hz as this is generally considered essential for high accuracy in EMG analysis, especially in the aspects of frequency analysis. On the other hand, it has been shown (Lariviére et al., 2005) that even with a considerably lower sampling rate of 256 Hz one can still get a feasible grasp on general muscular activity and occupation mechanical exposure from the data.

In addition, when performing electrophysiological signal processing, the right use of filtering is a delicate task. The 0.5 Hz high pass filter used in this study might have been too high, removing important low frequency delta oscillation components in the data. However, when reanalysis was performed following the 0.1 Hz filter yielded qualitatively very similar results.

Lastly, one has to address the limitations of subjective self-reports provided by study participants. Phenomenological research has shown that self-reports of untrained individuals, the same as were participating in our study, might not be valid. That means, feedback on personal motivation, perceived performance or side effect intensity would not reflect the actual experience of the person reporting asked. In fact, it is hard to control for bias in self-reports, even if feedback is given in form of a number from 1 to 7, it might be quite far away from the true perception of that person. On the other hand, self-reports can be a very sensible measure if used complementary to other behavioral measures, thus allowing a more profound insight into the first person perspective on the phenomenon at test, which too often is neglected.

5. Conclusion

In sum, even if not all performance tests yielded significant differences between treatment conditions, placebo administration could influence expectations and performance of healthy young individuals both in cognitive and physical terms: Placebo administration seems to increase muscular endurance rather than maximal isometric force. There was an indirect effect of placebo treatment on cognitive performance, namely via a more efficient resource allocation. A significant run x session interaction led to a drop in task effort (P3b amplitude) under placebo condition, but at the same time, performance level in the attention and working memory task remained constant, which might be explained by more efficient resource allocation under placebo treatment. Given the dissociation between P3a and P3b component in placebo response, one can speculate about the effects on norepinephrine activity by the placebo effect measured. In this study, there have been no indications that autonomic nervous system tone was affected by placebo treatment. Tendencies of subjective perception were largely corresponding with behavioral measures.

Insights about psychophysiological pathways of placebo responses have finally brought us closer to the understanding of old questions and theoretical concepts about interactions between conscious expectations, neural activity and physiology. In accordance with the enactive perspective of Varela et al. (1993), these insights emphasize that cognition (expectations and physiology) and environment (placebos) are closely intertwined and modulating each other.

Absence of disease makes studying PE in healthy participants a good model for researching interactions between environment, body and mind. In this model, one can easily test how conscious or subconscious expectations influence physiology and cognitive capacity.

In the future, adding more interdisciplinary perspectives on this psychobiological phenomenon will be very helpful in order to elucidate the pertinent mechanisms involved in even more detail and to find the optimum dosage, frequency and

interval of placebo usage for the general population. After all, numerous potential applications, also beyond the clinical setting, render placebo a constitutive tool, which can be used for improvement of health and performance.

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7. Appendix

7.1 Curriculum Vitae

Michael Kecht

School

06/2007	CJD Christophorusschule Berchtesgaden, Berchtesgaden, Germany **Graduation: "Abitur", grade: 2.0** Intensive Courses: Biology and English

Studies

10/2007 – 08/2010	Paris-Lodron University, Salzburg, Austria **Molecular Biology** Graduation: **Bachelor of Science, grade: 1.7** Bachelor Theses: 1st Thesis: Principles of translational recoding, grade 1.0, 2nd Thesis: Cloning in Biotechnology, grade 1.0
10/2010 – 01/2013	University of Vienna, Austria **Middle European International Master Programme in Cognitive Science** Graduation: **Master of Science, grade: 1.2** Master thesis "Cognitive and Physical Performance Changes Caused by Expectation of Enhancement "

Scholarships

10/2011 – 02/2012	Erasmus Scholarship by IEAC Austria, Exchange Semester in Ljubljana, Slovenia
03/2012 – 06/2012	support grant by the University of Vienna, for continuation of the Master's thesis as interdisciplinary research project in Ljubljana, Slovenia and for travel costs to present the work on FENS2012 and IK2012 conferences
03/2011 – 07/2011	Performance Scholarship by the University of Vienna, Grade 1.06
10/2011 - 02/2012	Performance Scholarship by the University of Vienna, Grade 1.11

Publications

Article:	Michael Oehler, Christian Reuter, Harald Schandara & Michael Kecht. (2011) The octave illusion revisit-

	ed - performance measurements for handedness categorization. Journal of the Acoustical Society of America, 130, 4, 2398 http://lib.bioinfo.pl/paper:21973791
Poster:	Kecht M.K., Minarikova B., Georgiev D., Bon J., Repovš G. & Bresjanac M. (2012), Physical and cognitive performance changes caused by expectation of enhancement. 8th Forum of Neuroscience, Barcelona http://fens.ekonnect.co/FENS_331/poster_35111/program.aspx
Article:	Michael Kecht, Barbora Minarikova, Christina Siserman (2012) The efficacy of criminal norms in regard to admissibility of testimonies in court proceedings, International Conference on the Efficiency of Legal Norms, Faculty of Law Dimitrie Cantemir, March 23-24, 2012, Cluj-Napoca, Romania, published in Editura Hamangiu, Cluj-Napoca, Romania.

Languages

German	native speaker
English	fluent
Spanish	'nivel inicial', D.E.L.E Diploma

Engagement and Hobbies

03/2004 – 12/2010	Honorary training and work as certified youth leader of the county Chiemgau in Bavaria, Germany. Organization and Leading of Youth Camps (Croatia, Austria and Germany)
12/2006 – today	Training and work as certified member of the German skiing and snowboarding instructor association.
Hobbies/Interests	Playing the guitar and jam sessions, improvisational theatre and staging, all kinds of winter sports, mountain climbing, jogging, slack line, Karate, Yoga, chess on tournament level, journeys and getting to know foreign cultures

References

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Dr. Michael Oehler	kontakt@michaeloehler.de

7.2 Exemplary BFI questionnaire

How I am in general

Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who *likes to spend time with others*? Please write a number next to each statement to indicate the extent to which **you agree or disagree with that statement.**

1 Disagree Strongly	**2** Disagree a little	**3** Neither agree nor disagree	**4** Agree a little	**5** Agree strongly

I am someone who…

1. _____ Is talkative
2. _____ Tends to find fault with others
3. _____ Does a thorough job
4. _____ Is depressed, blue
5. _____ Is original, comes up with new ideas
6. _____ Is reserved
7. _____ Is helpful and unselfish with others
8. _____ Can be somewhat careless
9. _____ Is relaxed, handles stress well.
10. _____ Is curious about many different things
11. _____ Is full of energy
12. _____ Starts quarrels with others
13. _____ Is a reliable worker
14. _____ Can be tense
15. _____ Is ingenious, a deep thinker
16. _____ Generates a lot of enthusiasm
17. _____ Has a forgiving nature
18. _____ Tends to be disorganized
19. _____ Worries a lot
20. _____ Has an active imagination
21. _____ Tends to be quiet
22. _____ Is generally trusting
23. _____ Tends to be lazy
24. _____ Is emotionally stable, not easily upset
25. _____ Is inventive
26. _____ Has an assertive personality
27. _____ Can be cold and aloof
28. _____ Perseveres until the task is finished
29. _____ Can be moody
30. _____ Values artistic, aesthetic experiences
31. _____ Is sometimes shy, inhibited
32. _____ Is considerate and kind to almost everyone
33. _____ Does things efficiently
34. _____ Remains calm in tense situations

35. _____ Prefers work that is routine

36. _____ Is outgoing, sociable

37. _____ Is sometimes rude to others

38. _____ Makes plans and follows through with them

39. _____ Gets nervous easily

40. _____ Likes to reflect, play with ideas

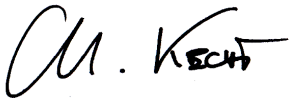
41. _____ Has few artistic interests

42. _____ Likes to cooperate with others

43. _____ Is easily distracted

44. _____ Is sophisticated in art, music, or literature

Ich habe mich bemüht, sämtliche Inhaber der Bildrechte ausfindig zu machen und ihre Zustimmung zur Verwendung der Bilder in dieser Arbeit eingeholt. Sollte dennoch eine Urheberrechtsverletzung bekannt werden, ersuche ich um Meldung bei mir.



Michael Kecht Wien, 07.03.2013