Oxazepam and cognitive reappraisal: a randomised experiment

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Abstract

Background: Cognitive reappraisal is a strategy for emotional regulation, important in the context of anxiety disorders. It is not known whether anxiolytic effects of benzodiazepines affect cognitive reappraisal.
Aims: We aimed to investigate the effect of 25 mg oxazepam on cognitive reappraisal.
Methods: Participants ($n = 33$) were randomised to oxazepam or placebo, and then underwent an experiment where they were asked to use cognitive reappraisal to upregulate or downregulate their emotional response to images with negative or neutral emotional valence. We recorded unpleasantness ratings, skin conductance, superciliary corrugator muscle activity, and heart rate. Participants completed rating scales measuring empathy (Interpersonal Reactivity Index, IRI), anxiety (State-Trait Anxiety Inventory, STAI), alexithymia (Toronto Alexithymia Scale-20, TAS-20), and psychopathy (Psychopathy Personality Inventory-Revised, PPI-R).
Results: Upregulation to negative-valence images in the cognitive reappraisal task caused increased unpleasantness ratings, corrugator activity, and heart rate compared to downregulation. Upregulation to both negative- and neutral-valence images caused increased skin conductance responses. Oxazepam caused lower unpleasantness ratings to negative-valence stimuli, but did not interact with reappraisal instruction on any outcome. Self-rated trait empathy was associated with stronger responses to negative-valence stimuli, whereas self-rated psychopathic traits were associated with weaker responses to negative-valence stimuli.
Conclusions: While 25 mg oxazepam caused lower unpleasantness ratings in response to negative-valence images, we did not observe an effect of 25 mg oxazepam on emotional reappraisal.

Introduction

Background

Cognitive reappraisal represents an explicit top-down regulatory mechanism in the processing of emotional stimuli [1]. In functional brain imaging studies, cognitive reappraisal has been associated with activity particularly in dorsolateral prefrontal cortex (dlPFC) and lateral orbitofrontal cortex (OFC) [2–6]. These areas are proposed to exert top-down control over emotional processing in limbic brain structures including the amygdala [2–7]. Cognitive reappraisal is important in psychiatric conditions involving anxiety [8–10], which may be associated with insufficient top-down control [9, 11]. One meta-analysis of fMRI studies found that patients with mood and anxiety disorders showed less activation than healthy controls during cognitive reappraisal in areas including the bilateral dorsomedial prefrontal cortex and the left ventrolateral prefrontal cortex [12]. Training in cognitive reappraisal can also be part of a treatment for depression, as well as other psychiatric conditions (reviewed in [13])

Benzodiazepines are anxiolytic drugs acting through $GABA_A$ receptors, which are pentameric ligand-gated ion channels composed of α, β, and γ subunits. Anxiolytic effects of benzodiazepines are likely mediated mainly by α-2 subunit containing $GABA_A$ receptors [14], which are highly expressed in the amygdala [15]. Sedative and anticonvulsant effects are likely mediated mainly by α-1 subunit containing $GABA_A$ receptors, which are expressed widely in the cerebral cortex [14–17]. It has been shown that increased activity in amygdala and insula associated to fear and anxiety processing are suppressed in a dose dependent manner after treatment with benzodiazepines in humans [7]. Anecdotally, bensodiazepines have been reported to be used to disinhibit criminal violent behavior [18–20]. We have previously tested the hypothesis that 20 mg oxazepam would inhibit empathy for pain, finding no conclusive evidence for such an effect [21]. Another possible explanation for instrumental use of bensodiazepines could be that they, often in combination with alcohol, reduce the ability to regulate emotional responses and thereby cause increased aggression. This would suggest an interaction between top-down regulatory mechanisms and treatment with bensodiazepines.

Thus, both cognitive reappraisal and benzodiazepines may be associated with inhibition of unpleasantness in response to negatively valenced emotional stimuli, and both act upon the amygdala. However, it is not known whether these regulatory processes interact or act independently on emotional processing.

We investigated the effects of 25 mg oxazepam in a study encompassing three different experiments targeting different types of emotional processing: emotional mimicry, empathy for pain, and emotional reappraisal. This paper reports results from the emotional reappraisal experiment. Results from the experiments on emotional mimicry and empathy for pain have been previously reported [21], and the primary findings were that 25 mg oxazepam did not have a major effect on emotional mimicry nor on empathy for pain. Cognitive reappraisal can be thought of as a higher-level top-down emotion regulating function, mechanistically distinct from the more bottom-up processes of emotional mimicry and empathy for pain.

Aims

We aimed to investigate effects of 25 mg oxazepam and cognitive reappraisal on emotion-related outcomes, hypothesising that an interaction would be observed where oxazepam reduced the effects of reappraisal. Additionally, we investigated interactions of personality traits related to empathy, psychopathy and anxiety with regulation instruction and stimulus valence.

Materials and Methods

Study design

This experiment formed part of a larger study on the effects of oxazepam on social emotional processes. For a detailed description, see [21]. Briefly, participants were randomised to 25 mg oxazepam or placebo in a double-blind between-groups design, and underwent experiments on emotional mimicry, empathy for pain, and cognitive reappraisal. This paper reports effects of oxazepam on cognitive reappraisal. The study was performed in two waves. Stimuli were balanced over regulation instructions using two different trial lists. Due to an error in randomisation in wave 1, stimulus images were not balanced between instructions to upregulate and downregulate emotional response. Therefore only data from wave 2 were analysed for the experiment on cognitive reappraisal.

Participants

As described in [21], participants were required to be right-handed, male, 18-45 years of age, to have no history of neurological or psychiatric disease including substance abuse, to speak and understand Swedish fluently, and not to be habitual consumers of nicotine. Furthermore, students of psychology, behavioural sciences, and medicine (past the 3rd semester) were not included, because training in medicine may cause a more detached attitude towards images of injured and sick people, which were used in the experiment, and because students of psychology and behavioural science may be prone to metacogitate and use different strategies for emotional regulation. We aimed for a sample size of $n = 40$, with 20 participants in each of the two treatment groups, based on pragmatic considerations. Participants were paid 500 SEK (approx. 50 Euro or 60 USD), subject to tax.

Stimuli and experimental paradigm

The experimental paradigm was adapted from [2]. Stimulus images were chosen from the International Affective Picture System (IAPS) [22]. Fig 1 shows stimulus presentation timing. Participants were asked to either upregulate or downregulate their emotional response by cognitive reappraisal, i.e. imagining different contexts for the situations shown in the images, such as a fictitious situation (downregulation) or something happening to someone close to them (upregulation). Participants were specifically instructed not to close their eyes or look away. After each stimulus, participants were asked to rate their perceived unpleasantness on a visual analog scale from 0 to 100. Before the experiment, participants underwent a demonstration session, and were then asked to explain the instructions back to the experimenter in order to ensure that the instructions were understood. Video clips were shown using the Presentation software (Neurobehavioral systems, Inc., Berkeley, CA, USA) on a computer screen. Stimulus presentation code is available at `https://doi.org/10.5281/zenodo.31480`. For a further verification that emotional regulation took place, we administered a recall test online, where participants were asked to say whether they recalled images from the experiment, as well as valence-matched images from the IAPS that had not been shown in the experiment. The data from the recall test were unfortunately lost when the online test platform upgraded their software.

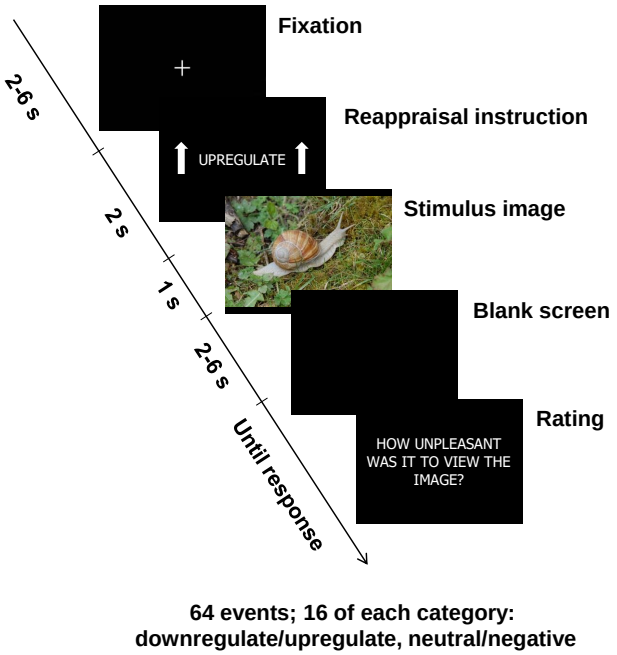

Fig 1. Experimental paradigm. The example stimulus image shown here was not part of the stimulus set.

Physiological measures

We recorded skin conductance, electromyographic (EMG) activity over the superciliary corrugator muscle, and heart rate, as described in [21].

Briefly, skin conductance responses were measured using Ag/AgCl finger electrodes (TSD203, Biopac Systems, Inc.), connected to a GSR100C amplifier (Biopac Systems, Inc.) with the following acquisitions settings: 5 $\mu\mho$/V, 1 Hz low-pass filter, and direct current. To remove non-physiological noise, data were further filtered in the Acqknowledge software using a low pass filter with a 1 Hz cutoff and 4000 coefficients and converted from direct to alternating current using an 0.05 Hz high pass filter. Responses were averaged over a time window of 2 seconds. The time window for analysis was chosen based on inspection of data.

EMG was measured following established guidelines [23], with 4 mm Ag-AgCl electrodes (EL254S, Biopac Systems, Inc.) connected to EMG100C amplifiers (Biopac Systems, Inc.) with the following acquisition settings: gain 500, low-pass filter 500 Hz, notch filter off, and high-pass filter 10 Hz. Sampling was at 1000 Hz. The signal was further filtered in the Acqknowledge software using a band pass filter of 30 to 300 Hz to remove signal not due to muscle activity. A band stop filter at 49 to 51 Hz was used to filter out line noise. Average rectified EMG signal was determined. Recordings were downsampled to 100 Hz in order to decrease file size, and data were exported as text files. Before analyses, recordings were further downsampled to 10 Hz using a loess curve in R. Responses were averaged over a time window of 2 seconds and log-transformed before statistical analysis, in order to better approximate a normal distribution. The time window for analysis was chosen based on inspection of data.

A 3-lead EKG was acquired using Ag/AgCl electrodes (EL503, Biopac Systems, Inc.) with ECG100 amplifiers (Biopac Systems, Inc.) with the following settings: gain 2000, mode R wave, 35HzLPN on, high-pass filter 0.5 Hz. Sampling was at 1000 Hz.

Recordings were downsampled to 100 Hz in order to decrease file size, and data were exported from the Acqknowledge software as text files. Heart rate was derived from raw curves by a peak finding algorithm in R. Estimated heart rate of <40 or >200 beats per minutes was rejected (0.2% of data). For each event, heart rate was normalised to the 2 seconds preceding regulation instruction onset and averaged over a time window from 3 to 5 seconds from regulation instruction onset. The time window for analysis was chosen based on inspection of data.

Rating scales

Rating scales in this study have been described in [21]. The interpersonal reactivity index (IRI) has four subscales which measure different dimensions of trait empathy: empathic concern (EC), perspective taking (PT), personal distress (PD) and fantasy (FS) [24, 25]. The IRI has been validated in a Swedish context [26], although the four-factor structure could not be replicated. Instead, EC formed one factor and PT, PD and FS together formed another factor. For this reason, we have not analysed differences between IRI subscales.

The state-trait anxiety inventory (STAI) has a state and a trait subscale [27]. We used a non-validated Swedish translation with which we have considerable experience, and which can be found in [28]. The state subscale (S) was administered before the experiment, and then again at the end of the experiment.

The Toronto Alexithymia Scale-20 (TAS-20) measures alexithymia, a construct thought to represent difficulties in identifying and describing one's own emotions. It has three subscales: difficulty identifying feelings, difficulty describing feelings and externally oriented thinking [29]. We analysed only total scores. The scale has been validated in Swedish [30].

The psychopathy personality inventory-revised (PPI-R) assesses psychopathic traits [31, 32]. It contains eight content scales, which have been organized into a two-factor structure, encompassing the factors fearless dominance (FD; reflecting social poise, fearlessness and stress immunity) and self-centred impulsivity (SCI; reflecting impulsivity, irresponsibility and egocentricity). It also contains a subscale particularly reflecting lack of empathy (coldheartedness, C), which typically does not load highly on either factor. The Swedish version of the PPI-R has been validated based partly on the data collected in this study [33].

Analyses and data

Data and analysis code for this paper are openly available at `https://doi.org/10.5281/zenodo.3236077`. In order to preserve anonymity, participants' age and educational background have been omitted from the published dataset. All analyses were made with R [34], using the packages **RCurl** [35] to read data from GitHub, **quantmod** [36] to find EKG R wave peaks, **nlme** [37] to build mixed-effects models, **effects** [38] to get confidence intervals on estimates, and **RColorBrewer** [39] for graphing. Mixed-effects models have been used throughout unless otherwise indicated.

To investigate interaction effects of self-rated personality traits with stimulus valence and reappraisal instruction, a separate regression model was run with each rating scale, in which interactions between the scale score and valence and reappraisal instruction, respectively, were specified. Scale scores were z-transformed to yield standardized regression coefficients.

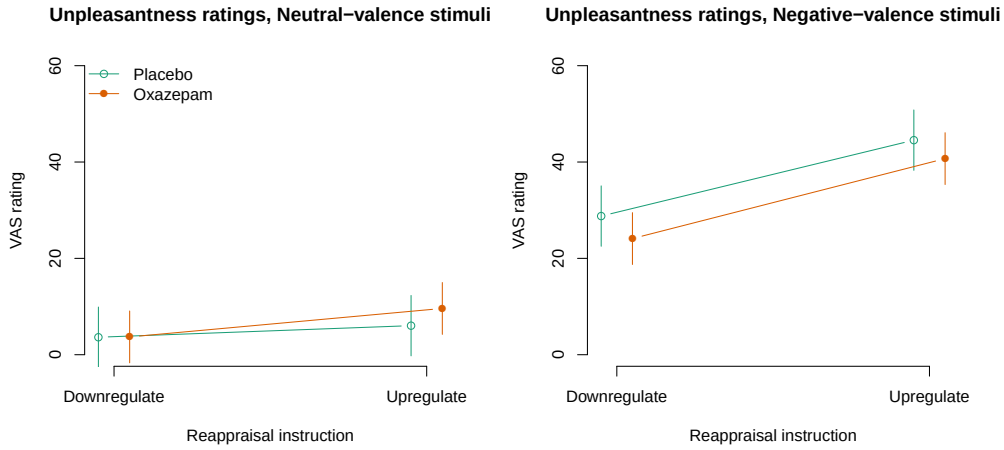

Fig 2. Rated unpleasantness: model estimates with 95% confidence intervals.

Results

Participants

Thirty-nine participants were randomised. Six did not perform the reappraisal experiment since they reported having previously participated in other experiments involving viewing images likely to be from the same IAPS stimulus set. The final sample included 33 participants, of which 13 were in the placebo group (median age 22, range 18-44) and 20 in the oxazepam group (median age 22.5, range 18-41).

Unpleasantness ratings

We investigated the interactions between upregulation, negative stimulus valence, and oxazepam treatment on unpleasantness ratings. The three-way interaction was -2.7 [95% CI -9.1, 3.8], $p = 0.42$ (Fig 2). The two-way interaction between upregulation and negative stimulus valence was in the expected direction (12.0 [8.8, 15.2], $p < 0.0001$). The two-way interaction between negative stimulus valence and oxazepam treatment showed that lower unpleasantness was reported to negative-valence stimuli in the oxazepam group compared to the placebo group (-6.1 [-9.3, -2.7], $p = 0.0002$), consistent with an anxiolytic effect. The two-way interaction between upregulation and oxazepam treatment was 2.2 [-1.0, 5.4], $p = 0.19$. The main effect of negative stimulus valence was 28.8 [27.2, 30.4], $p < 0.0001$. The main effect of upregulation was 10.2 [8.6, 11.8], $p < 0.0001$, and the main effect of oxazepam treatment was -1.2 [-9.3, 6.9], $p = 0.76$.

Skin conductance

Skin conductance was measured as an indicator of autonomic activity. Fig 3 shows time-courses of skin conductance. The time window for signal extraction was chosen based on inspection of time courses.

The three-way interaction between negative stimulus valence, upregulation, and oxazepam treatment was 0.002 [-0.015, 0.019], $p = 0.79$ (Fig 4). The two-way interaction between negative stimulus valence and upregulation was -0.006 [-0.014, 0.003], $p = 0.18$. The two-way interaction between negative stimulus valence and oxazepam treatment was 0.002 [-0.006, 0.011], $p = 0.57$. The two-way interaction between upregulation and oxazepam treatment was 0.001 [-0.011, 0.013], $p = 0.84$. The

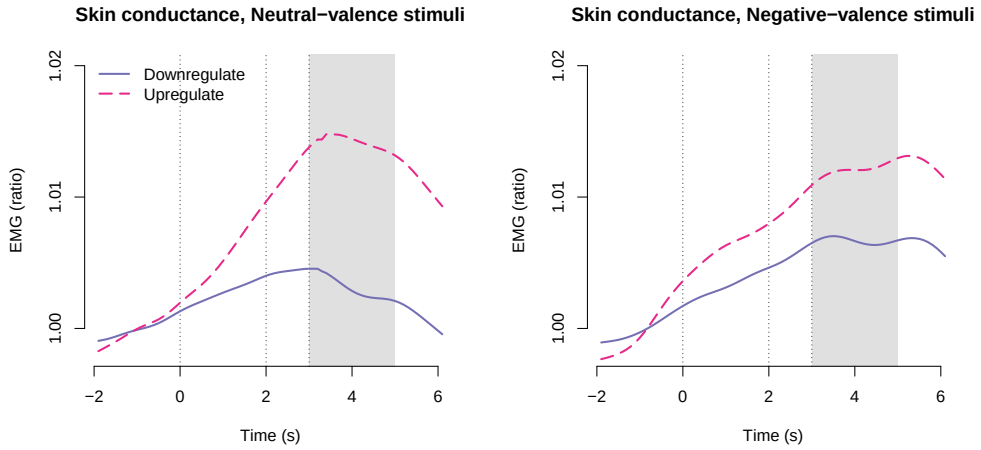

Fig 3. Skin conductance time-courses across treatment groups. The first vertical line shows regulation instruction onset; the second vertical line shows stimulus image onset; and the third vertical line shows stimulus image offset. The shaded gray area shows the time window from which responses were averaged for statistical modelling.

main effect of negative stimulus valence was 0.001 [-0.004, 0.005], $p = 0.78$. The main effect of upregulation was 0.007 [0.003, 0.011], $p = 0.001$, as expected. The main effect of oxazepam was -0.001 [-0.007, 0.005], $p = 0.71$.

Corrugator activity

Activity of the superciliary corrugator muscle was measured as an indicator of negative emotion. Fig 5 shows time-courses of corrugator EMG activity. The time window for signal extraction was chosen based on inspection of time courses.

The three-way interaction between negative stimulus valence, upregulation, and oxazepam treatment was -0.031 [-0.201, 0.138], $p = 0.72$ (Fig 6). The two-way interaction between negative valence and upregulation was 0.108 [0.023, 0.192], $p = 0.01$, as expected. The two-way interaction between negative stimulus valence and oxazepam treatment was -0.055 [-0.140, 0.030], $p = 0.20$. The two-way interaction between upregulation and oxazepam treatment was 0.026 [-0.059, 0.110], $p = 0.55$. The main effect of negative stimulus valence was 0.061 [0.019, 0.103], $p = 0.005$. The main effect of upregulation was 0.069 [0.026, 0.111], $p = 0.002$. The main effect of oxazepam treatment was -0.066 [-0.168, 0.037], $p = 0.20$.

Heart rate

Heart rate was measured as an indicator of autonomic activity. Fig 7 shows time-courses of heart rate changes, demonstrating deceleration following stimulus presentation. The time window for signal extraction was chosen based on inspection of time courses.

The three-way interaction between negative valence, upregulation, and oxazepam treatment was -0.013 [-0.037, 0.011], $p = 0.29$, Fig 8. The two-way interaction between negative valence and upregulation was 0.012 [0.000, 0.024], $p = 0.04$, as expected. The two-way interaction between negative valence and oxazepam treatment was -0.001 [-0.013, 0.011], $p = 0.90$. The two-way interaction between upregulation and oxazepam treatment was -0.001 [-0.013, 0.010], $p = 0.82$. The main effect of negative valence was -0.002 [-0.008, 0.004], $p = 0.51$. The main effect of upregulation was 0.003 [-0.003, 0.009],

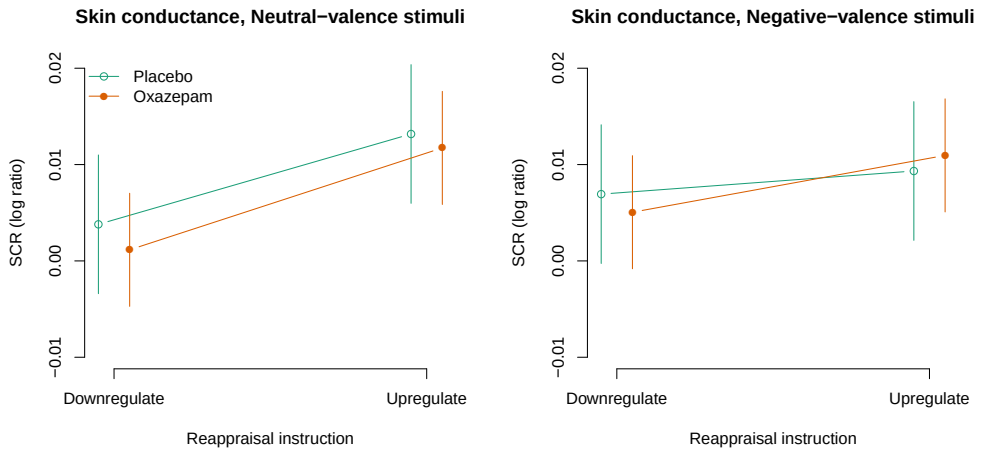

Fig 4. Skin conductance: model estimates with 95% confidence intervals.

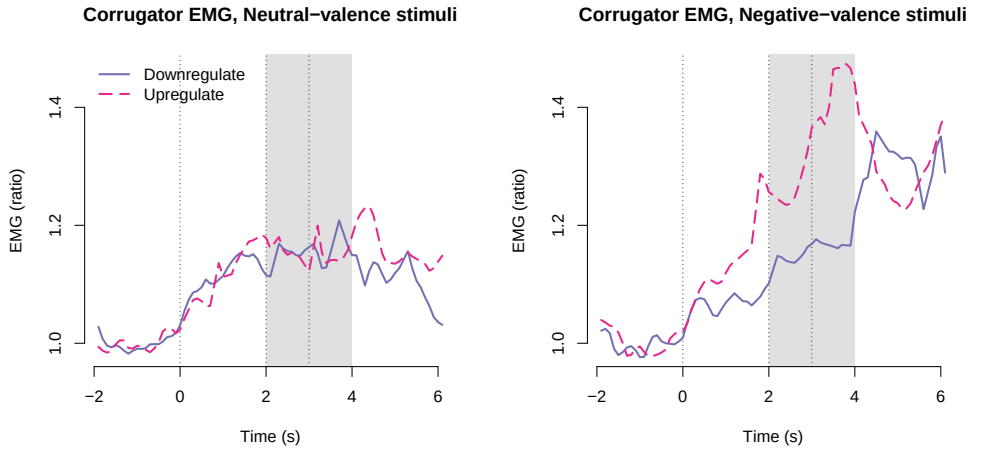

Fig 5. Corrugator EMG time-courses across treatment groups. The first vertical line shows onset of the instruction; the second vertical line shows stimulus image onset; and the third vertical line shows stimulus image offset. The shaded gray area shows the time window from which responses were averaged for statistical modelling.

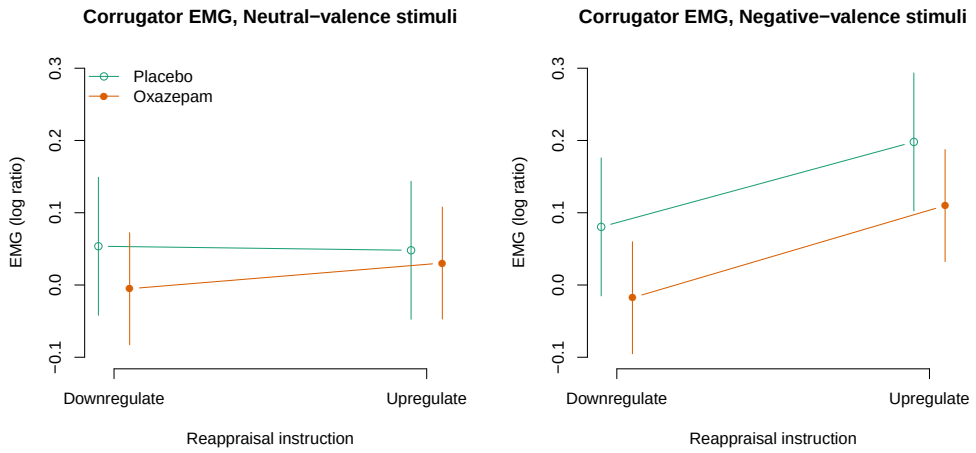

Fig 6. Corrugator EMG responses: model estimates with 95% confidence intervals.

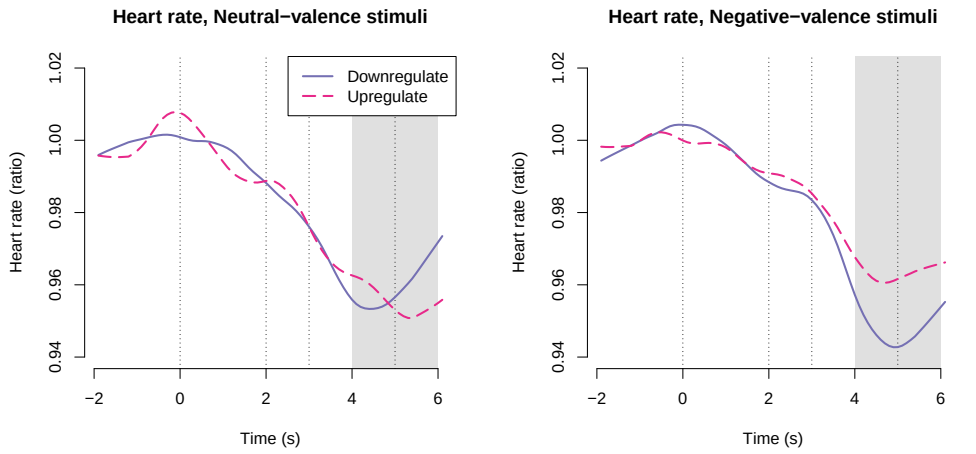

Fig 7. Heart rate time-courses across treatment groups. The first vertical line shows onset of the instruction; the second vertical line shows stimulus image onset; and the third vertical line shows stimulus image offset. The shaded gray area shows the time window from which responses were averaged for statistical modelling.

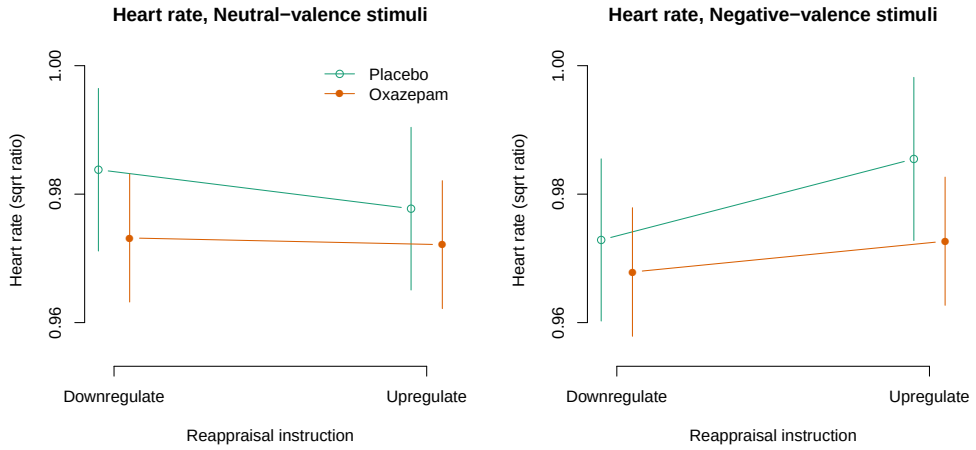

Fig 8. Heart rate: model estimates with 95% confidence intervals.

$p = 0.39$. The main effect of oxazepam treatment was -0.009 [-0.021, 0.004], $p = 0.19$, Fig 8.

Self-rated personality traits and cognitive reappraisal

Exploratory analyses of self-rated personality traits as predictors for cognitive reappraisal showed that empathy subscales IRI-EC, IRI-PT, and IRI-F were associated with higher rated unpleasantness to negative-valence images, whereas empathy subscale IRI-PD and all three subscales of the psychopathy personality inventory-revised (PPI-R) were associated with lower rated unpleasantness to negative-valence images (Fig 9). For skin conductance, no rating scales showed interactions with stimulus valence nor instruction with regard to skin conductance (Fig 9). For corrugator activity, the coldheartedness (C) subscale of the PPI-R, was associated with higher activity to negative-valence stimuli, and the perspective taking subscale of the IRI and the Fearless Dominance subscale of the PPI-R were associated with higher activity in the upregulate condition, whereas the Toronto Alexithymia Scale-20 (TAS-20) was associated with lower activity in the upregulate condition (Fig 9). For heart rate, coldheartedness (PPI-R-C) was associated with lower heart rate in response to negative-valence images (Fig 9).

Discussion

In this study, we examined the effect of 25 mg oxazepam on cognitive reappraisal. In summary, we found that upregulation of negative-valence images caused increased unpleasantness ratings, corrugator activity, and heart rate compared to downregulation, confirming the validity of the paradigm. Oxazepam caused lower ratings of unpleasantness to negative stimuli, but no interaction between oxazepam and reappraisal was observed.

As we have previously described in a report on the empathy for pain paradigm using the full sample of this experiment, [21], efficacy of drug effects was verified by longer response times and lower rated anxiety after the experiment in the oxazepam group. As noted above, upregulation of negative-valence images caused increased unpleasantness ratings, corrugator activity, and heart rate. Upregulation to both negative- and neutral-valence images also caused increased skin conductance responses. These findings

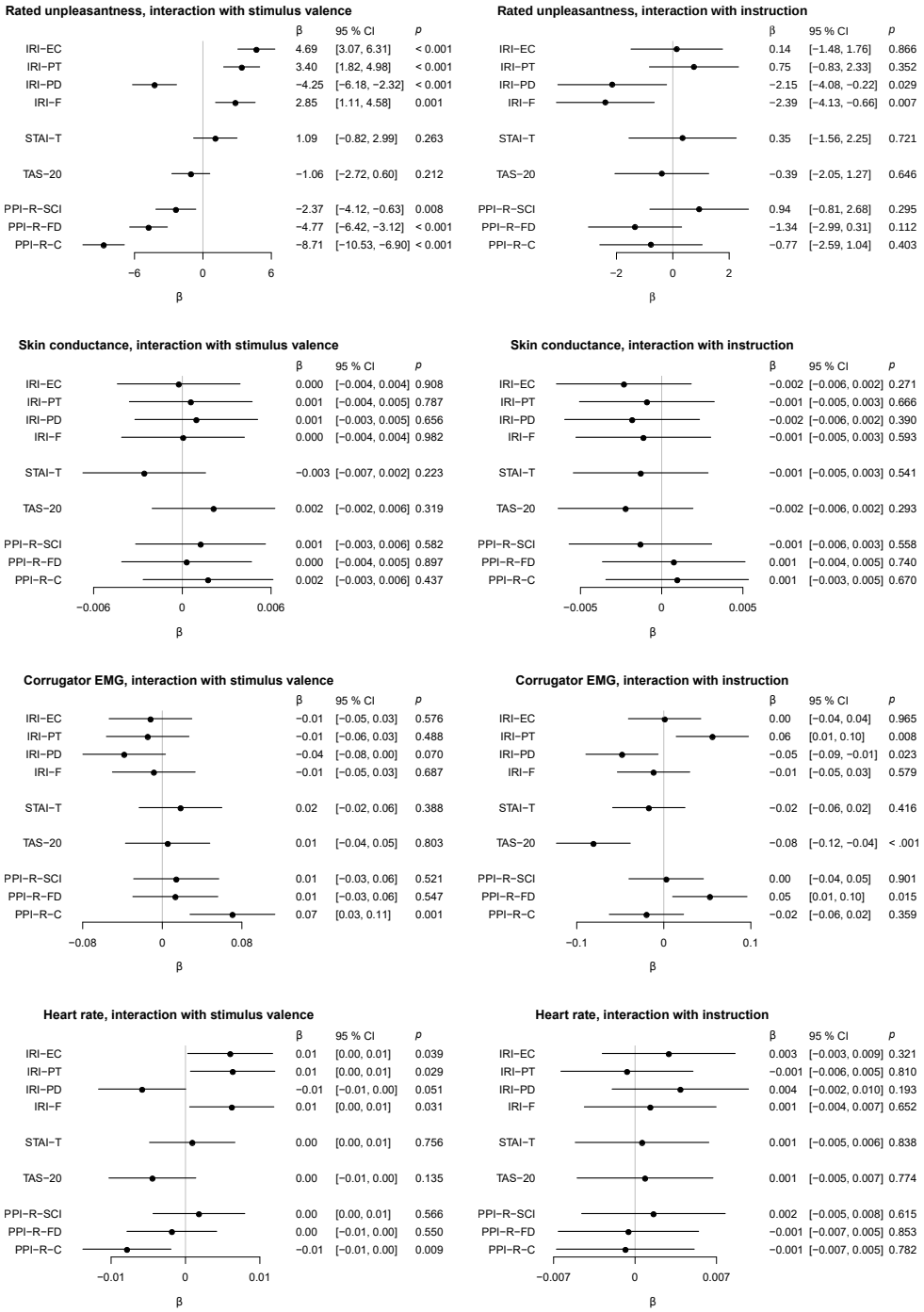

Fig 9. Interaction effects of self-rated personality traits with stimulus valence and reappraisal instruction. Effects shown are standardized regression coefficients with 95% confidence intervals.

confirm that the experimental paradigm was effective and that the drug reached a biological effect in the oxazepam group, providing an appropriate setting to test the effect of oxazepam on cognitive reappraisal. Ratings of unpleasantness may be affected by demand effects. As argued by Ray et al. [40], it is more convincing to measure both self-report and autonomic indices of emotional responses in reappraisal experiments, since they are sensitive to partly different sets of biases. In particular, autonomic responses are likely to be less affected by demand characteristics. In line with this reasoning, our finding that upregulation by cognitive reappraisal was associated with increased skin conductance responses further supports the validity of the paradigm, and is consistent with earlier findings [5].

Oxazepam caused lower ratings of unpleasantness to negative stimuli, but did not show any noteworthy interaction with cognitive reappraisal on any of our outcomes, contrary to the main hypothesis. These results indicate that 25 mg oxazepam does not have a major effect on cognitive reappraisal. However, the effect on emotional stimuli (without regulation) indicates that oxazepam modulates the affective experience of negative stimuli. This finding is consistent with an earlier finding from our group, where i.v. midazolam reduced perceived unpleasantness of negative-valence IAPS images [41]. It has been suggested that this effect could be caused by a general decrease in anxiety due to inhibited amygdala-dependent emotional processing [7].Although the same physiological measurements were not used, our results contrast somewhat with previous reports that 20 mg oxazepam did not modulate affective ratings or event-related potentials in response to emotional stimuli [42], and that neither 15 nor 30 mg oxazepam affected the fear-potentiated startle response [43].

Cognitive reappraisal works through reappraising emotional stimuli in different ways. Functional imaging studies have shown that dorsolateral prefrontal and lateral orbitofrontal cortices are specifically involved in these processes [2, 4–6]. It has also been shown that these prefrontal processes directly interact with processing of emotional information in brain regions such as the amygdala. Since we showed effects of cognitive reappraisal on affective ratings and physiological measures but no interaction with bensodiazepines our data suggests that these regulatory processes do not interact but work in parallel. Therefore, our data do not corroborate the prediction that top-down regulatory mechanisms are suppressed by bensodiazepines, arising from the disinhibition theory of criminal violent behavior as suggested by [19, 20].

Associations between on the one hand self-rated empathy, anxiety, alexithymia, psychopathy, and on the other hand cognitive reappraisal, have not been widely investigated. One study has investigated the association of alexithymia to event-related potentials (ERP:s) during cognitive reappraisal, and found that higher alexithymia in a sample of healthy humans was associated with smaller ERP:s [44]. The strongest associations between rating scales and experimental outcomes were observed for self-rated unpleasantness. This may be explained by the similar nature between these self-rated measures, as opposed to physiological measures.

The generalizability of our results is limited by the nature of the sample, consisting of only male participants, most with ongoing or completed university education. The limited size of the sample also precludes strong conclusions. Furthermore, the choice of time windows for analyses of physiological signals is based on the observed data, which may introduce bias. Further work should use independent samples to define time windows of interest and to test hypotheses. It is also an open question whether different results would be seen with a higher dose of oxazepam or with another benzodiazepine.

Conclusion

While 25 mg oxazepam caused lower rated unpleasantness in response to negative valence images, we did not observe an effect of 25 mg oxazepam on emotional reappraisal.

Author contributions

Conceived of study: GN, ST, AG, MI, PP. Collected data: GN, ST. Analysed data: GN. Interpreted results: GN, ST, AG, AO, KS, KH, MK, MI, PP. Drafted manuscript: GN. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Braunstein LM, Gross JJ, Ochsner KN. Explicit and implicit emotion regulation: a multi-level framework. Social Cognitive and Affective Neuroscience. 2017 Oct;12(10):1545–1557. Available from: `https://academic.oup.com/scan/article/12/10/1545/4158838`.

2. Golkar A, Lonsdorf TB, Olsson A, Lindstrom KM, Berrebi J, Fransson P, et al. Distinct Contributions of the Dorsolateral Prefrontal and Orbitofrontal Cortex during Emotion Regulation. PLoS ONE. 2012 Nov;7(11):e48107. Available from: `http://dx.doi.org/10.1371/journal.pone.0048107`.

3. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, et al. Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. Cerebral Cortex (New York, NY). 2014 Nov;24(11):2981–2990. Available from: `http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193464/`.

4. Kanske P, Heissler J, Schönfelder S, Bongers A, Wessa M. How to regulate emotion? Neural networks for reappraisal and distraction. Cerebral Cortex (New York, NY: 1991). 2011 Jun;21(6):1379–1388.

5. Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S. Regulation of emotional responses elicited by threat-related stimuli. Human Brain Mapping. 2007 May;28(5):409–423.

6. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Neural mechanisms of emotion regulation: Evidence for two independent prefrontal-subcortical pathways. Neuron. 2008 Sep;59(6):1037–1050. Available from: `http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2742320/`.

7. Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. Archives of General Psychiatry. 2005 Mar;62(3):282–288.

8. Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, et al. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. Biological Psychiatry. 2011 Mar;69(6):564–573.

9. Manber Ball T, Ramsawh HJ, Campbell-Sills L, Paulus MP, Stein MB. Prefrontal Dysfunction during Emotion Regulation in Generalized Anxiety and Panic Disorder. Psychological medicine. 2013 Jul;43(7):1475–1486. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4308620/.

10. Rabinak CA, MacNamara A, Kennedy AE, Angstadt M, Stein MB, Liberzon I, et al. Focal and aberrant prefrontal engagement during emotion regulation in veterans with posttraumatic stress disorder. Depression and anxiety. 2014 Oct;31(10):851–861. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4141895/.

11. Bishop SJ. Neurocognitive mechanisms of anxiety: an integrative account. Trends in Cognitive Sciences. 2007 Jul;11(7):307–316.

12. Picó-Pérez M, Radua J, Steward T, Menchón JM, Soriano-Mas C. Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2017 Jun;79(Pt B):96–104.

13. Bowins B. Cognitive regulatory control therapies. American Journal of Psychotherapy. 2013;67(3):215–236.

14. Nutt D. GABAA receptors: subtypes, regional distribution, and function. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2006 Apr;2(2):S7–11.

15. Hörtnagl H, Tasan RO, Wieselthaler A, Kirchmair E, Sieghart W, Sperk G. Patterns of mRNA and protein expression for 12 GABAA receptor subunits in the mouse brain. Neuroscience. 2013 Apr;236:345–372. Available from: http://www.sciencedirect.com/science/article/pii/S0306452213000249.

16. Rudolph U, Crestani F, Möhler H. GABAA receptor subtypes: dissecting their pharmacological functions. Trends in Pharmacological Sciences. 2001 Apr;22(4):188–194. Available from: http://www.sciencedirect.com/science/article/pii/S0165614700016461.

17. Odano I, Halldin C, Karlsson P, Varrone A, Airaksinen AJ, Krasikova RN, et al. [18F]Flumazenil binding to central benzodiazepine receptor studies by PET: – Quantitative analysis and comparisons with [11C]flumazenil –. NeuroImage. 2009 Apr;45(3):891–902. Available from: http://www.sciencedirect.com/science/article/pii/S1053811908012445.

18. Dåderman AM, Lidberg L. Flunitrazepam (Rohypnol) abuse in combination with alcohol causes premeditated, grievous violence in male juvenile offenders. The Journal of the American Academy of Psychiatry and the Law. 1999;27(1):83–99.

19. Dåderman AM, Fredriksson B, Kristiansson M, Nilsson LH, Lidberg L. Violent behavior, impulsive decision-making, and anterograde amnesia while intoxicated with flunitrazepam and alcohol or other drugs: a case study in forensic psychiatric patients. Journal of the American Academy of Psychiatry and the Law Online. 2002 Jun;30(2):238–251. Available from: http://www.jaapl.org/content/30/2/238.

20. Dåderman AM, Fredriksson B, Nilsson LH, Kristiansson M, Lidberg L. The abuse of a sleeping pill that contains the active substance flunitrazepam (FZ)–for example, Rohypnol–and the effects of FZ intoxication, such as enhanced violence and disturbed memory. Journal of the American Academy of Psychiatry and the Law Online. 2004 Dec;32(4):467–468. Available from: http://www.jaapl.org/content/32/4/467.

21. Nilsonne G, Tamm S, Golkar A, Sörman K, Howner K, Kristiansson M, et al. Effects of 25 mg oxazepam on emotional mimicry and empathy for pain: a randomized controlled experiment. Open Science. 2017 Mar;4(3):160607. Available from: http://rsos.royalsocietypublishing.org/content/4/3/160607.

22. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical report A-8. 2008;.

23. Fridlund AJ, Cacioppo JT. Guidelines for Human Electromyographic Research. Psychophysiology. 1986;23(5):567–589. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8986.1986.tb00676.x/abstract.

24. Davis M. A multidimensional approach to individual differences in empathy. JSAS Catalog of Selected Documents in Psychology. 1980;10(85).

25. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. Journal of Personality and Social Psychology. 1983;44(1):113–126.

26. Cliffordson C. Parents' Judgments and Students' Self-Judgments of Empathy. European Journal of Psychological Assessment. 2001 Jan;17(1):36–47. Available from: http://econtent.hogrefe.com/doi/abs/10.1027//1015-5759.17.1.36.

27. Spielberger C, Gorsuch R, Lushene P, Vagg P. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Inc., Palo Alto, CA; 1983.

28. Nilsonne G. Data-and-analysis-code-Oxazepam-and-emotion: Release for publication. Zenodo; 2016. Available from: https://zenodo.org/record/60385#.WWLIbYgrJnI.

29. Bagby RM, Parker JDA, Taylor GJ. The twenty-item Toronto Alexithymia scale—I. Item selection and cross-validation of the factor structure. Journal of Psychosomatic Research. 1994 Jan;38(1):23–32. Available from: http://www.jpsychores.com/article/0022-3999(94)90005-1/abstract.

30. Simonsson-Sarnecki M, Lundh LG, Törestad B, Bagby RM, Taylor G, Parker J. A Swedish Translation of the 20-item Toronto Alexithymia Scale: Cross-validation of the Factor Structure. Scandinavian Journal of Psychology. 2000 Mar;41(1):25–30. Available from: http://onlinelibrary.wiley.com/doi/10.1111/1467-9450.00167/abstract.

31. Lilienfeld SO, Andrews BP. Development and Preliminary Validation of a Self-Report Measure of Psychopathic Personality Traits in Noncriminal Population. Journal of Personality Assessment. 1996 Jun;66(3):488–524. Available from: http://dx.doi.org/10.1207/s15327752jpa6603_3.

32. Benning SD, Patrick CJ, Hicks BM, Blonigen DM, Krueger RF. Factor structure of the psychopathic personality inventory: validity and implications for clinical assessment. Psychological Assessment. 2003 Sep;15(3):340–350.

33. Sörman K, Nilsonne G, Howner K, Tamm S, Caman S, Wang HX, et al. Reliability and Construct Validity of the Psychopathic Personality Inventory-Revised in a Swedish Non-Criminal Sample – A Multimethod Approach including Psychophysiological Correlates of Empathy for Pain. PLOS ONE. 2016 Jun;11(6):e0156570. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0156570.

34. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2015. Available from: http://www.R-project.org/.

35. Lang DT. RCurl: General network (HTTP/FTP/...) client interface for R; 2015. R package version 1.95-4.6. Available from: http://CRAN.R-project.org/package=RCurl.

36. Ryan JA. quantmod: Quantitative Financial Modelling Framework; 2015. R package version 0.4-4. Available from: http://CRAN.R-project.org/package=quantmod.

37. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. nlme: Linear and Nonlinear Mixed Effects Models; 2015. R package version 3.1-120. Available from: http://CRAN.R-project.org/package=nlme.

38. Fox J. Effect displays in R for generalised linear models. Journal of Statistical Software. 2003;8(15):1–27.

39. Neuwirth E. RColorBrewer: ColorBrewer Palettes; 2014. R package version 1.1-2. Available from: http://CRAN.R-project.org/package=RColorBrewer.

40. Ray RD, McRae K, Ochsner KN, Gross JJ. Cognitive Reappraisal of Negative Affect: Converging Evidence From EMG and Self-Report. Emotion (Washington, DC). 2010 Aug;10(4):587–592. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4106258/.

41. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing–induced expectations of anxiety relief activate a generalized modulatory network. Neuron. 2005 Jun;46(6):957–969.

42. Olofsson JK, Gospic K, Petrovic P, Ingvar M, Wiens S. Effects of oxazepam on affective perception, recognition, and event-related potentials. Psychopharmacology. 2011 May;215(2):301–309. Available from: https://link.springer.com/article/10.1007/s00213-010-2141-z.

43. Baas JMP, Grillon C, Böcker KBE, Brack AA, Morgan CA, Kenemans JL, et al. Benzodiazepines have no effect on fear-potentiated startle in humans. Psychopharmacology. 2002 May;161(3):233–247.

44. Walker S, O'Connor DB, Schaefer A. Brain potentials to emotional pictures are modulated by alexithymia during emotion regulation. Cognitive, Affective, & Behavioral Neuroscience. 2011 Dec;11(4):463–475. Available from: https://link-springer-com.proxy.kib.ki.se/article/10.3758/s13415-011-0042-1.