RESEARCH ARTICLE

REVISED Effects of concomitant benzodiazepines and antidepressants long-term use on perspective-taking [version 2; peer review: 1 approved]

Ana R. Gonçalves[1], Márcia Soares[1], Helena Garcez[1], Carina Fernandes[1], Mariana R. Pereira[1], Celeste Silveira[1,2], João Marques-Teixeira[1], Fernando Barbosa[1]

[1]Faculty of Psychology and Education Sciences, University of Porto, Porto, Portugal
[2]São João University Hospital Center, Porto, Portugal

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Abstract

Background: Benzodiazepines and antidepressants are known to alter responses to empathic pain when used alone, however the effects of their combined use on the perspective-taking facet of empathy are unknown. In order to examine the effects of concomitant benzodiazepines and antidepressants long-term use on perspective-taking, we analyzed behavioral and neural changes on perspective-taking ability using event-related potentials.
Methods: To this purpose, 13 long-term concomitant benzodiazepines and antidepressants users and 13 healthy controls performed a task designed to assess affective perspective-taking with simultaneous EEG recording.
Results: The behavioral results revealed similar performance between groups. The neural results showed no significant differences between groups for the N170 and late positive potential (LPP) components. These results seem to suggest that long-term use of benzodiazepines and antidepressants together does not affect perspective-taking abilities nor the processing of related information.
Conclusions: The concomitant benzodiazepines and antidepressants long-term use seem to preserve the perspective-taking ability of social cognition.

Keywords

Empathy, ERP, performance, psychotropic medication, social cognition

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Approval Status ✓

	1
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1. **Helena Hartmann**, University Hospital Essen, Essen, Germany

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Ana R. Gonçalves (a.s.ribeiro.g@gmail.com)

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REVISED **Amendments from Version 1**

The main differences between the two versions of the manuscript are the information added to clarify aspects addressed in the introduction and discussion. In the new version, it was also emphasized the limitation of having a low sample size when drawing conclusions.

Any further responses from the reviewers can be found at the end of the article

Introduction

Empathy is involved in several aspects of social cognition. It has been proposed to notably contribute to prosocial behavior[1,2] and to regulate aggression.[3] Empathy is defined as the ability to experience and understand the feelings of another person, while also understanding the origin of the feelings, that is, whose belong to whom.[4] Previous research based on psychometric data has defined different facets of empathy: empathic concern, personal distress, perspective-taking and fantasy.[5,6]

Perspective-taking enables us to make inferences, understand and foresee other's mental and emotional states – an ability known as Theory of Mind[7] - as well as to have empathic ability. The ability to correctly infer the emotional states of another person is known as emotional perspective-taking and is determinant for the success of social interactions.[8]

The use of benzodiazepines has been reported to facilitate aggressive[9] and violent behavior,[10,11] leading to suspicion of their inhibitory effects on empathic responses. Bearing this in mind, Nilsonne and colleagues[12] investigated the effects of oxazepam on empathic responding. Using an experiment on empathy for pain, the authors found that oxazepam did not inhibit empathic responses to others' pain.[12] Benzodiazepines are often added to antidepressants in initial depression treatment but previous research showed that the simultaneous use is long term.[13] Nonetheless, a previous study suggested that antidepressant treatment reduces behavioral and neural responses to pain empathy[14] and may have a cumulative effect to that caused by the use of benzodiazepines.

To our knowledge, these are the only studies examining the effects of benzodiazepines and antidepressants, when used alone, on empathy. Furthermore, there is no information on the neural temporal dynamics of empathy processes under the use of such medication. Thus, the effects of medication interactions used for long periods on the perspective-taking facet of empathy are still unknown. The current study examines the effects of concomitant benzodiazepines and antidepressants long-term use on perspective-taking using event-related potentials (ERPs). To this purpose, we used a task previously adapted by our group[15] in which scenarios presenting two persons engaged in social interactions, depicting emotional and neutral scenes, are shown to participants. In each scenario, one person has the face masked. In the next display, a target facial expression of emotion (FEE) is presented and participants are asked to judge whether this FEE is congruent or not with the emotion expected to be portrayed by the masked person. Thus, in each scenario, participants must infer the affective mental state of the masked intervener. Then, to an accurate decision, participants also have to compare the inferred emotion to the emotion presented in the target FEE, and decide wether they were congruent or incongruent. Using this experimental manipulation, we will be able to investigate perspective-taking abilities through the behavioral performance and, with simultaneous EEG recording, to assess how these abilities modulate two ERP components - the N170 and the late positive potential (LPP). These components are known to be typically influenced by the affective and evaluative congruency.

The N170 is a negative deflection usually peaking at ~170 ms post-stimulus in occipito-temporal sites. This component seems to reflect the earliest stage of facial structure encoding[16] and is sensitive to the emotional content of a face.[17,18] Concerning the influence of context, higher N170 amplitudes are usually recorded in congruent trials when pictures are used as contextual stimuli.[19–22]

The LPP is a positive deflection usually peaking at 300-700 ms after the stimulus onset in centro-parietal sites.[23] This component represents facilitated attention to emotional stimuli and has larger amplitudes after emotionally arousing pictures in comparison to neutral ones.[24] In the present study, the congruency between a prime and a target is manipulated, and previous studies using a similar experimental manipulation, reported that LPP indexes the processing of affective or evaluative congruency, and exhibits larger amplitudes to incongruent targets compared to congruent ones.[24] Furthermore, cognitive appraisal and motivated attention,[25] as well as morally good actions[26] and helping scenes[27] also modulate the LPP component.

The research on this field is essential considering that benzodiazepines and antidepressants are the most prescribed drugs in the world[28,29] despite their unwanted effects (e.g., psychomotor, and cognitive impairments; see Ref. 30). It is common to prescribe benzodiazepines and antidepressants simultaneously in initial depression treatment, however it has been previously reported that the simultaneous use extends beyond the initial period and becomes long term.[13] Benzodiazepines act at the limbic system, including at the thalamic and hypothalamic levels of the central nervous system[31] through $GABA_A$ receptors.[32] Antidepressants were shown to increase the activation of dorsolateral, dorsomedial and ventrolateral prefrontal cortices and to decrease the activation of the amygdala, hippocampus, parahippocampal region, ventral anterior cingulate cortex, orbitofrontal cortex, and insula.[33] Since some of these structures are involved in perspective-taking processes,[34] we may expect impaired performance of long-term concomitant benzodiazepines and antidepressants users on our perspective-taking task. Furthermore, considering that it was previously found that subjects from a clinical sample took longer to complete an emotional perspective-taking task, besides showing poorer performance than healthy controls,[35,36] we analyzed reaction times to clarify if they were affected in our study. Regarding electrophysiological results, as we expected a decreased perspective-taking ability in the group of long-term concomitant benzodiazepines and antidepressants users, we anticipated that N170 and LPP modulations would be absent in this group. Additionally, neurocognitive measures were collected to explore whether performance on the perspective-taking task is related to cognitive performance.

Methods

Participants

A total of 60 participants were recruited from the community and local University to two groups: a long-term concomitant benzodiazepines and antidepressants users group (experimental) and a control group, matched on age and years of formal education. The experimental group consisted of subjects who had a minimum period of concomitant benzodiazepines and antidepressants use of one year. We excluded participants with scores inferior to 22 (cutoff for mild cognitive impairment[37]) in the Montreal Cognitive Assessment (MoCA[38]; n = 1), as well as participants who reported uncorrected visual impairments (n = 1), history of brain injury and neurological diagnosis (n = 2). Participants reporting use of psychotropic medication besides benzodiazepines and antidepressants (n = 2), and psychiatric diagnosis aside from anxiety and depression (except severe conditions rendering study participation impossible) (n = 2) were also excluded from the experimental group. We also excluded participants from the control group if they reported use of psychotropic medication (n = 13) and psychiatric diagnosis (n = 4). Additionally, 9 participants dropped out the study at the end of the neuropsychological assessment. Thus, the final sample was composed of 13 experimental subjects (all female; M_{age} = 44.1, SD = 10.0; $M_{years\ of\ education}$ = 15.9, SD = 2.4) and 13 control subjects (12 female; M_{age} = 46.5, SD = 10.9; $M_{years\ of\ education}$ = 16.9, SD = 4.9). They each gave written, informed consent and received EUR 20 (gift card). The study was approved by the local Ethics Committee.

Instruments and tasks

Self-report measures

Anxiety and depression traits were measured by the Hospital Anxiety and Depression Scale (HADS[39]; Portuguese version by Pais-Ribeiro *et al.*[40]), and psychopathological symptomatology by the Brief Symptom Inventory (BSI[41]; Portuguese version by Canavarro[42]).

Neuropsychological measures

Executive functioning was assessed using the Trail Making Test (TMT[43]; normative data by Cavaco *et al.*[44]), and the INECO Frontal Screening (IFS[45]; Portuguese version by Moreira *et al.*[46]). Semantic fluency and phonemic fluency tests were used to assess non-motor processing speed, language production and executive functions (see Ref. 47; Portuguese versions by Cavaco *et al.*[48]). Short-term memory was assessed by the Corsi Block-Tapping Task (CBTT[49]).

Emotional perspective-taking task

This task was adapted from a previous fMRI study that assessed perspective-taking[8] as described in our prior work[15] examining perspective-taking ability during an ERP experiment. Succinctly, the protocol used by Derntl *et al.*[8] was adapted according to experimental designs of previous studies addressing contextual congruency.[19–23,50,51] Contextual congruency implies the matching between a target facial expression of emotion (FEE) and the emotion portrayed by a masked face in a previous scenario.[15] Thus, participants had to recall perspective-taking abilities to accurately judge the contextual congruency: they had to see the scenario and examine it from another's perspective, and then judge whether a FEE shown next was congruent or not with the emotion expected to be portrayed by the masked person.

To this purpose, participants viewed 360 pictures representing scenes of two persons engaged in social interactions. Each scenario presented one of the actors' faces masked, and participants were instructed to infer the respective emotional expression. The scenarios depicted emotional (anger, fear, disgust, sadness, happiness) and neutral scenes and all actors were adult Caucasians. After the scenario display, a target FEE was presented, and participants were asked to judge it as congruent or incongruent with the inferred FEE of the masked person. Next, an unlimited duration screen with the response options was presented until key press. During this screen, participants used two response buttons held in the right and left hand. Participants were asked to respond only during this response screen, to prevent overlap of preparatory response potentials with the ERP components of interest. The structure of each trial is depicted in Figure 1.

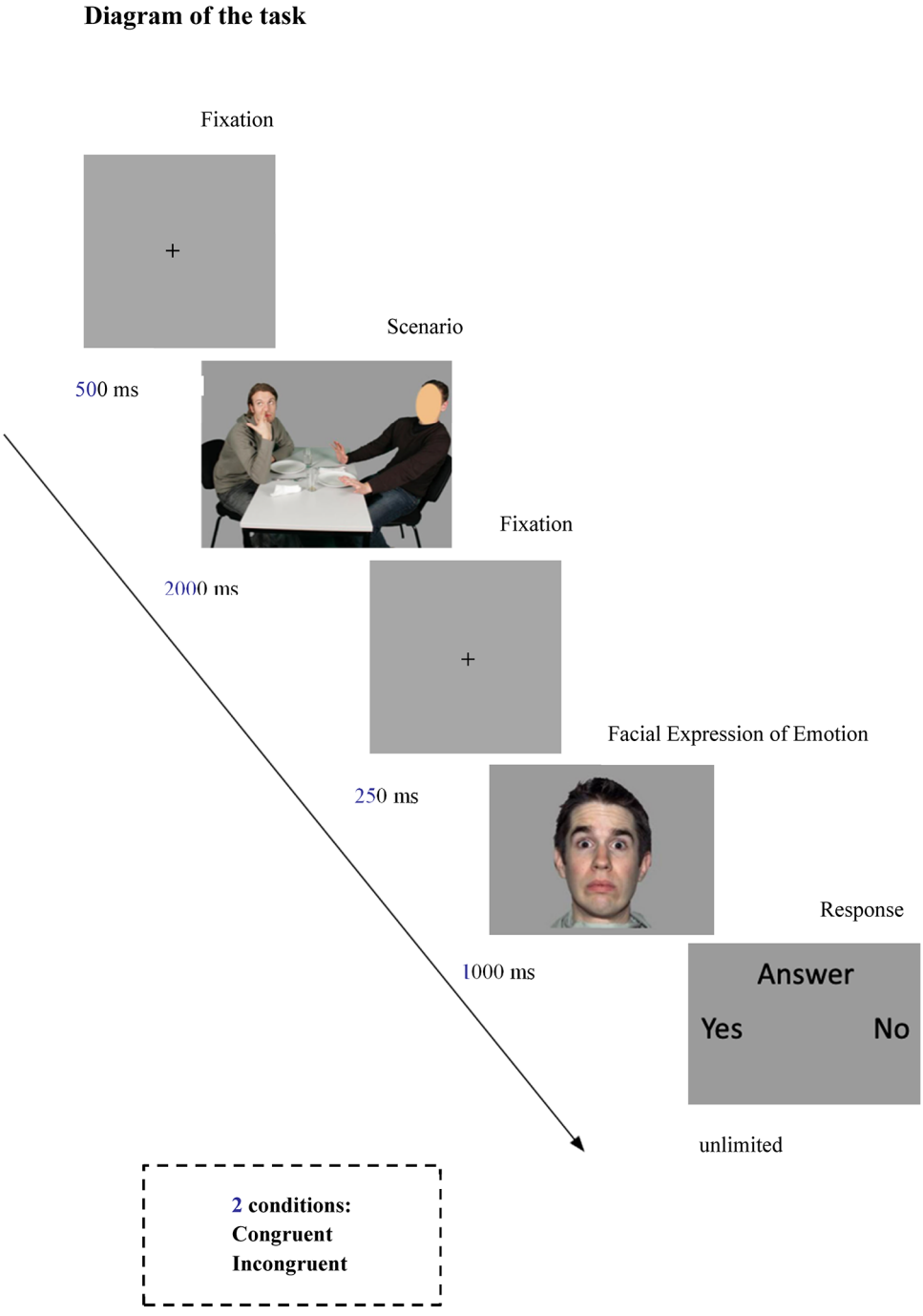

Figure 1. Schematic representation of a trial of the perspective-taking task.

As the original set of stimuli,[8] ten scenarios for each emotional condition were included, with six repetitions for each one. For congruent conditions, the FEE was randomly selected from all alternative actors with the congruent emotion; the incongruent conditions included FEE selected from all the incongruent alternatives. This results in 30 congruent trials and 30 incongruent trials for each emotional condition. The FEE was selected from the NimStim Face Stimulus Set,[52] picking the five most accurately identified facial expressions for each emotional category (see Ref. 52) which led to 30 female and 30 male facial stimuli. Participants viewed the images on a 17-in. screen from a distance of 115 cm, with 6.67° × 8.55° visual angle, and a refresh rate of 60 Hz. E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, USA) was used to control the experiment and collect responses. After a block of six practice trials, participants completed two experimental blocks of 180 trials each, with a pause between them.

Procedures

All participants were tested individually in two experimental sessions to avoid fatigue effects. In the first session, a semi-structured interview and the MoCA were conducted to assess inclusion criteria. The remaining neuropsychological tests and self-report measures were then administered in a random order between participants. Participants meeting the inclusion criteria were invited to participate on a second session, in which the emotional perspective-taking task was performed simultaneously to EEG recording. This second session was part of a larger research protocol, demanding all experimental tasks to be performed in random order. After the placement of the EEG cap, participants read the instructions and completed a practice block.

EEG recording and processing

The eletroencephalographic (EEG) data were recorded on the acquisition software V4.5.2 (2008, Electrical Geodesics Inc., Eugene, OR, USA – EGI) using a 128-electrode Hydrocel Geodesic Sensor Net, connected to a Net Amps 300 amplifier (EGI). Impedances were kept below 50 kOhm for all electrodes since this is a high-input impedance system. Data were recorded with a sampling rate of 500 Hz, filtered with a notch filter of 50 Hz and the electrodes were referenced to the vertex (Cz).

The EEG raw data were pre-processed in the EEGLAB version 13,[53] a MATLAB toolbox (2017, The Math-works Inc., Natick, MA, USA). Continuous EEG signal was downsampled to 250 Hz, bandpass filtered (0.2−30 Hz), and submitted to an Independent Components Analysis (ICA) decomposition. Eyeblinks, saccades, and cardiac activity artifacts were corrected, by subtracting the corresponding Independent Component activity from the data, followed by visual inspection to ensure the correction did not alter the signals outside the time windows of the artifacts. Channels with artifacts were interpolated (up to a maximum of 10% of the sensors) using the spherical spline interpolation method.[54] The EEG signal was re-referenced to the average of all electrodes. EEG records were segmented into epochs (-200 to 800 ms) time-locked to the onset of the target FEE and visually inspected for manual artifact rejection. Trials in which participants gave incorrect responses were also excluded. All epochs were baseline corrected (200 ms pre-stimulus) and averaged by congruency (congruent, incongruent) and emotion (anger, fear, disgust, sadness, happiness, neutral).

According to previous studies, and visual inspection of ERP grand-average and topographical maps, three time windows and three regions of interest (ROIs)[2] were chosen for statistical analysis. The higher amplitude of the N170 component is exhibited bilaterally at occipitotemporal regions, precisely at P7/P8 and PO7/PO8, being more marked at the inferior locations as P9/P10 and PO9/P10 (Rossion and Jacques 2008). A negative maximum over these regions was recorded in our topographical maps, leading us to set a ROI containing these and a cluster of surrounding electrodes, to increase the signal-to-noise ratio.[55,56] Accordingly, the peak amplitudes for the N170 were extracted in the [140, 240] ms time window after FEE onset, at right (electrodes 83, 84, 89, 90 [PO8], 91, 95 [P10], 96 [P8]) and left (70, 66, 69, 65 [PO7], 64 [P9], 58 [P7], 59) ROIs. Regarding the LPP component, other studies reported that its higher amplitude occurs over centro-parietal sites such as CPz and Pz.[23] Our topographical maps are in accordance with this result, so we extracted the mean LPP amplitudes at the centro-parietal ROI (54, 55 [CPz], 61, 62 [Pz], 78, 79). The time window of this component was divided into an early (LPPe; 300–500 ms after FEE onset) and a late component (LPPl; 500–700 ms after FEE onset) given its temporally broad distribution (e.g., Ref. 50).

Statistical analysis

Student's t-tests were used to analyze group differences in neuropsychological performance and self-report measures. Whenever necessary, non-parametric tests were performed. Perspective-taking results were obtained from accuracy rates (percentage of correct responses in relation to the total number of trials) calculated by participant and condition. The effects of emotion, congruency, and group on perspective-taking results were analyzed in a mixed ANOVA. The group (experimental, control) was used as between-participants factor, whereas emotion (anger, fear, disgust, sadness, happiness, neutral) and congruency (congruent, incongruent) were used as within-participants factors. The same analysis was performed for reaction times.

The electrophysiological data were analyzed by mixed factors ANOVAs with group as between-participants factor, and emotion and congruency as within-participant factors. For N170, the hemisphere (left, right) was also used as within-participant factor.

To test the influence of cognitive abilities in behavioral performance and ERPs modulation, a Linear Regression Model was computed for each group. Scores of cognitive tests (raw scores) in which differences between groups were detected were entered as main predictors of behavioral measures and N170, and LPPs modulation (independent models). For N170, LPPe and LPPl modulation, the model was applied to each electrode or electrode cluster examined in the ERP data analysis. The model was computed only for the experimental group since it was our group of interest. To further explore and clarify the results, the analysis was extended to the control group whenever necessary.

The threshold for statistical significance was set at $\alpha = .05$, and the p-values reported for t-tests are from one-tailed tests. Statistical analysis was performed using SPSS 24 (IBM Corp., Armonk, NY, USA). Violations of sphericity in ANOVA were corrected via the Greenhouse-Geisser method.

Results

Neuropsychological results

Neuropsychological data analysis revealed no differences between groups in IFS, CBTT, TMT, PF, nor SF (all $p > .313$). However, significant group differences were observed on depression, $t(24) = -3.735$, $p < .002$, anxiety, $t(24) = -3.156$, $p = .004$, and psychopathological symptomatology, $t(24) = -4.450$, $p < .001$. Experimental subjects had higher scores in these self-report measures (see Table 1).

Behavioral results

Accuracy rates and reaction times are shown in Table 2. These were examined using a mixed factors ANOVA. The results showed that experimental and control subjects were equally accurate in their responses, $F(1, 24) = 0.68$, $p = .417$. However, a main effect of emotion, $F(5, 120) = 28.2$, $p < .001$, $\eta^2_p = 0.541$, $\varepsilon = 1.000$, revealed accuracy rates significantly higher following scenarios portraying happiness (all $p < .001$), sadness (all $p < .033$), and neutral scenes (all $p < .027$), without significant differences between the latter ($p > .998$). Scenarios portraying anger, disgust, and fear elicited similar accuracy rates (all $p > .988$). We also found a significant emotion x group interaction, $F(5, 120) = 3.32$, $p = .008$, $\eta^2_p = .121$. However, none of the post-hoc comparisons achieved significance (all $p > .066$). A significant emotion x congruency interaction, $F(5, 120) = 9.31$, $p < .001$, $\eta^2_p = .280$, was found and post-hoc comparisons revealed higher accuracy rates for congruent condition portraying disgust ($p < .001$). No other significant interactions emerged (all $F < 0.78$, $p > .387$).

Regarding reaction times, no significant differences were found between the groups $F(1, 24) = 2.22$, $p = .149$. Also, no main effects were found for emotion, $F(5, 120) = 1.21$, $p = .309$, or congruency, $F(1, 24) = 0.91$ $p = .350$, factors. The analysis also showed that none of the interactions – emotion x group, congruency x group, emotion x congruency, and emotion x congruency x group – was statistically significant for reaction times (all $p > .150$).

Table 1. Mean (and SD) values of neuropsychological tests of the participants.

	Control (n = 13)	Experimental (n = 13)	t	p
Neuropsychological data				
MoCA	27.3 (1.7)	25.2 (2.2)		
IFS	23.3 (2.3)	23.7 (3.5)	-0.33	.372
CBTT	16.0 (3.9)	15.1 (3.5)	0.63	.266
TMT	52.1 (28.9)	50.9 (25.5)	0.11	.457
Phonemic fluency	42.2 (15.3)	36.5 (12.4)	1.03	.156
Semantic fluency	20.1 (6.3)	20.2 (6.4)	-0.03	.488
HADS depression	3.3 (2.1)	9.2 (5.2)	-3.75	<.001*
HADS anxiety	6.2 (3.1)	11.0 (4.5)	-3.16	.002*
BSI	29.6 (15.4)	79.2 (37.1)	-4.45	<.001*

Note. MoCA: Montreal Cognitive Assessment; IFS: Institute of Cognitive Neurology Frontal Screening; CBTT: Corsi Block-Tapping Task; TMT: Trail Making Test; HADS: Hospital Anxiety and Depression Scale; BSI: Brief Symptom Inventory.
*Significant differences.

Table 2. Means (and SD) values for accuracy rates (%) and reaction times (ms) in the emotional perspective-taking task for the two groups.

	Accuracy		Reaction times	
	Control	Experimental	Control	Experimental
Congruent condition				
Anger	70.0 (13.5)	72.8 (11.0)	881.68 (538.73)	676.91 (521.40)
Disgust	85.4 (9.19)	85.6 (10.8)	798.49 (329.11)	636.89 (440.25)
Fear	78.4 (15.9)	77.4 (14.9)	821.35 (257.62)	633.78 (361.37)
Happiness	96.4 (3.96)	93.3 (5.62)	820.64 (307.38)	557.93 (283.28)
Neutral	90.0 (10.3)	83.8 (10.2)	923.64 (418.41)	681.38 (561.03)
Sadness	79.0 (22.4)	85.1 (12.3)	802.24 (291.10)	716.40 (480.28)
Incongruent condition				
Anger	74.8 (18.6)	86.2 (9.2)	862.06 (335.53)	709.56 (532.32)
Disgust	67.9 (15.0)	71.0 (12.4)	996.10 (522.22)	684.06 (394.38)
Fear	72.0 (17.7)	81.2 (14.4)	821.49 (241.28)	641.67 (412.37)
Happiness	93.6 (6.03)	90.4 (12.00)	939.34 (518.20)	535.59 (302.02)
Neutral	81.2 (12.3)	80.8 (7.33)	809.28 (293.66)	643.18 (441.79)
Sadness	82.1 (11.9)	88.2 (9.96)	880.17 (322.19)	632.21 (391.22)

The Linear Regression analysis was significant for accuracy rates of scenarios portraying happiness in control subjects $F(5, 7) = 10.9$, $p = .002$. Anxiety (Adj $R^2 = .712$, $\beta = -.42$, $p = .035$) and psychopathological symptomatology (Adj $R^2 = .712$, $\beta = -.53$, $p = .008$) were main predictors of accuracy rates for happiness scenarios. For participants from the experimental group, the model was not significant (all $p > .234$).

Electrophysiological results

Peak amplitudes for N170 component are presented in Table 3 and mean amplitude for LPPs components are presented in Table 4.

Table 3. Means (and SD) for N170 peak amplitudes (μV) by group and condition.

	Control		Experimental	
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Congruent condition				
Anger	-2.56 (2.21)	-2.81 (2.77)	-3.17 (2.83)	-4.54 (3.17)
Disgust	-3.39 (2.53)	-3.66 (2.91)	-4.40 (3.72)	-4.72 (3.04)
Fear	-4.13 (2.49)	-4.49 (3.22)	-3.36 (3.40)	-4.16 (2.44)
Happiness	-2.93 (2.70)	-3.22 (2.91)	-3.22 (3.61)	-4.89 (3.40)
Neutral	-3.72 (1.93)	-3.22 (3.04)	-2.94 (2.82)	-4.18 (2.37)
Sadness	-3.89 (2.29)	-4.05 (2.82)	-4.10 (4.31)	-4.72 (3.24)
Incongruent condition				
Anger	-2.96 (2.75)	-3.18 (3.33)	-3.48 (3.22)	-4.22 (2.52)
Disgust	-3.00 (3.04)	-3.01 (3.03)	-3.37 (3.92)	-4.12 (3.34)
Fear	-3.19 (3.07)	-3.22 (3.41)	-3.76 (4.03)	-4.57 (3.31)
Happiness	-2.93 (2.70)	-3.22 (2.91)	-3.22 (3.61)	-4.89 (3.40)
Neutral	-3.56 (2.27)	-3.92 (2.83)	-3.54 (3.58)	-4.32 (3.48)
Sadness	-4.05 (2.36)	-3.95 (2.85)	-3.83 (3.21)	-5.33 (2.98)

Table 4. Means (and SD) for LPPs mean amplitudes (μV) by group and condition.

	Control		Experimental	
	LPPe	LPPl	LPPe	LPPl
Congruent condition				
Anger	2.13 (2.22)	3.63 (2.95)	1.40 (1.78)	2.43 (2.31)
Disgust	2.00 (2.56)	3.72 (3.46)	2.08 (1.21)	2.77 (1.38)
Fear	1.92 (2.49)	3.18 (2.79)	2.20 (1.15)	2.89 (1.40)
Happiness	1.85 (2.71)	4.00 (3.12)	1.38 (1.51)	2.18 (2.09)
Neutral	1.59 (2.13)	3.82 (2.76)	1.04 (1.12)	2.01 (1.26)
Sadness	1.88 (2.46)	3.74 (3.42)	1.80 (1.50)	2.43 (1.40)
Incongruent condition				
Anger	0.96 (2.40	2.96 (3.14)	0.99 (1.57)	2.01 (1.63)
Disgust	0.98 (2.88)	2.11 (2.81)	0.38 (2.26)	1.44 (2.21)
Fear	1.37 (1.89)	3.06 (2.67)	1.00 (1.71)	1.90 (2.05)
Happiness	1.85 (2.71)	4.00 (3.12)	1.38 (1.51)	2.18 (2.09)
Neutral	1.87 (2.18)	3.47 (2.79)	0.92 (1.51)	1.77 (1.81)
Sadness	1.73 (2.42)	3.46 (2.61)	1.50 (1.32)	2.52 (1.99)

The repeated measures ANOVA revealed no significant differences on the N170 amplitude between groups, $F(1, 22) = 0.33$, $p = .571$. A main effect of emotion emerged, $F(5, 110) = 2.60$, $p = .029$, $\eta^2_p = .106$, $\varepsilon = .782$, but the main effects of congruency and hemisphere were not significant (all $F < 1.96$). Pairwise comparisons revealed that faces portraying sadness elicited higher N170 amplitudes than faces portraying anger ($p = .050$) and neutral faces ($p = .012$). Additionally, the analysis showed that none of the interactions was statistically significant (all $p > .150$).

For the LPPe component, no significant differences were found on the mean amplitude between groups, $F(1, 22) = 0.22$, $p = .647$. A main effect of emotion was not found on the LPPe mean amplitude, $F(5, 110) = 1.15$, $p = .338$, but the main effect of congruency was significant $F(1, 22) = 18.5$, $p < .001$, $\eta^2_p = .457$, $\varepsilon = .984$. Additionally, a significant emotion x congruency interaction emerged, $F(5, 110) = 4.32$, $p = .004$, $\eta^2_p = .164$. Pairwise comparisons revealed that congruent conditions elicited higher LPPe amplitudes than incongruent conditions ($p < .001$) (Figure 2). No other significant interactions emerged (all $F < 0.95$, $p > .435$).

Regarding the LPPl, the pattern of results found was similar to the LPPe: no significant differences were found on the mean amplitude between groups, $F(1, 22) = 1.80$, $p = .194$; the main effect of emotion was not significant, $F(5, 110) = 1.59$, $p = .168$, but a main effect of congruency emerged, $F(1, 22) = 12.5$, $p = .002$, $\eta^2_p = .363$, $\varepsilon = .923$. The analysis also revealed a significant emotion x congruency interaction, $F(5, 110) = 2.81$, $p = .038$, $\eta^2_p = .113$. Pairwise comparisons revealed that congruent conditions elicited higher LPPl amplitudes than incongruent conditions ($p = .002$) (Figure 2). No other significant interactions emerged (all $F < 1.92$, $p > .096$).

The Linear Regression model was neither significant for N170 (all $p > .089$) nor LPPe (all $p > .056$) components in both groups. The model was significant for LPPl amplitudes in control subjects, $F(5, 6) = 5.36$, $p = .026$. Anxiety was a marginally main predictor of LPPl amplitudes for congruent conditions (Adj $R^2 = .543$, $\beta = -.504$, $p = .054$). For experimental subjects, the model was not significant (all $p > .680$).

Discussion

In the present study, concomitant benzodiazepines and antidepressants users and control subjects were presented with scenarios presenting two persons (one person with the face masked) engaged in social interactions, depicting emotional and neutral scenes, and asked to judge whether a FEE shown next was congruent or not with the emotion expected to be portrayed by the masked person.

Our results did not reveal group differences in perspective-taking ability, contrary to what we expected. Nonetheless, these results are consistent with the neural responses, revealing no differences in the processing of perspective-taking information as we will discuss later. The only studies[12,14] examining the effects of benzodiazepines and antidepressants

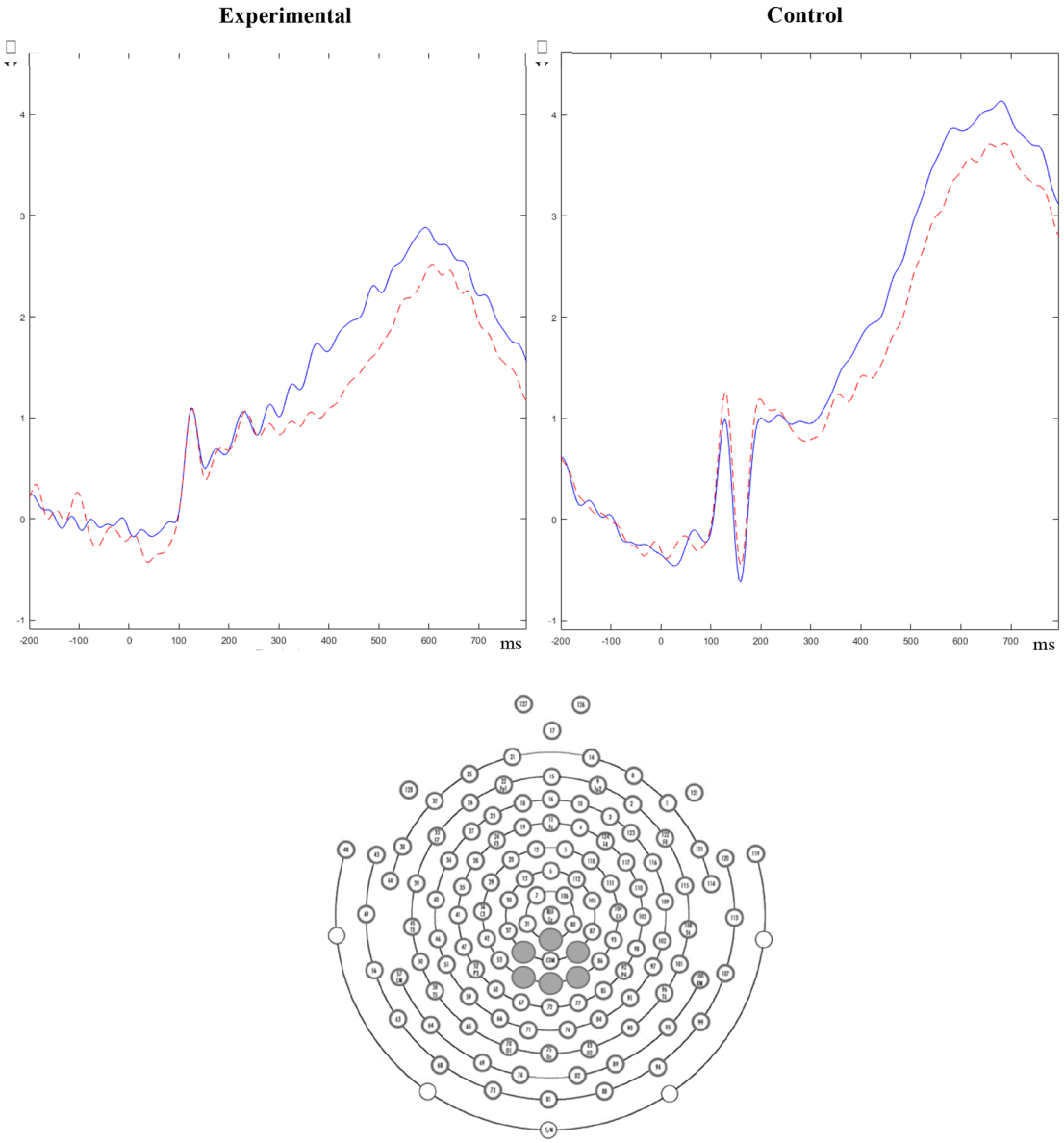

Figure 2. Grand-average of LPPe (300–500 ms) and LPPl (500–700 ms) for each group. Solid lines (blue) = congruent condition, broken lines (red) = incongruent condition.

on empathy did it for each class of drug isolated, using an experiment on empathy for pain. One study examined the effect of one single administration of oxazepam on empathy for pain and showed that empathic responses to other's pain were not inhibited.[12] Another study examined the effect of a three months antidepressant therapy on the responses to an empathy for pain task, in patients with major depressive disorder.[14] The results suggested that antidepressant treatment reduces behavioral and neural responses to pain empathy.[14] Bearing in mind that the ability of identifying FEE is required in the present task, we should mention the results of a previous meta-analysis by our group.[57] The meta-analysis examining how benzodiazepines administration affects the identification of FEE showed that participants receiving benzodiazepines were less accurate at identifying FEE of anger compared with those receiving placebo.[57] The identification of the remaining facial expressions (disgust, sadness, fear, surprise, and happiness) appears to be unaffected by benzodiazepines administration. However, these studies are methodologically far from our study which makes any comparison of the results impossible.

A main effect of emotion emerged consistent with the results of a previous study conducted by our group[15]: greater accuracies were reported for scenarios portraying happiness, sadness, and neutral scenes. Similar to the identification of happy faces,[58–60] happiness scenarios seem to be recognized more accurately than any other scenarios.

The current sample of concomitant benzodiazepines and antidepressants users scored higher in self-report measures of anxiety, depression, and psychopathological symptomatology. Anxiety and psychopathological symptomatology predicted accuracy rates for happiness scenarios in control subjects. This result was unexpected since it was not found in our previous study.[15] Furthermore, a meta-analysis[61] examining the boundary conditions of threat-related attentional biases in anxiety showed that a significant bias also occurred with stimuli outside awareness. Additionally, the bias is present in different types of anxious populations, including nonclinical individuals, and is not observed in non anxious individuals. This attentional bias in anxious individuals may account for higher accuracy rates when identifying emotional situations.[61] However, our results showed accuracy rates predicted by anxiety and psychopathological symptomatology only in control subjects and regarding happiness scenarios. Here we should consider that ceiling effects could have account for these results. In fact, ceiling effects have been known to hinder solid interpretations of the results, especially for facial expressions of happiness.[62,63]

Regarding electrophysiological data, we did not find significant differences between groups in the N170 component, but a main effect of emotion emerged similar to the pattern found in behavioral data. Furthermore, previous studies found a N170 modulated by emotion[64,65] providing evidence that early face processing can reflect processing of the emotional expression. In accordance with our previous study,[15] this component was not modulated by the congruency between the emotional contexts and the target's FEE. As noted by the authors,[15] this was unexpected since previous studies using pictures as contexts reported a systematically higher N170 in congruent trials.[19–22] However, a congruency modulation in N170 was previously not found in studies using verbal instead of visual stimuli.[50,51]

Consistent with our previous work,[15] the results obtained in the LPPs were similar in the early and late time-windows, revealing higher amplitudes in congruent than in incongruent trials. This pattern is opposite to the one reported by previous studies using context-target congruency tasks, i.e., larger LPPs after incongruent FEE.[50,66] However, while higher LPP amplitudes elicited by incongruent trials were reported in tasks requiring an evaluative congruity between primes and facial[23,67] or verbal targets,[68] our task required attending the scenes, inferring the mental state of the masked interveners, and deciding if the FEE displayed after the scene matched the one previously inferred. The recognition of the masked person's emotion in the stimuli displayed by the target FEE may explain the increased amplitudes to congruent stimuli since the LPP is also modulated by the explicit recognition of stimuli, exhibiting larger amplitudes in response to recognized stimuli *vs.* new.[69,70]

Noteworthy, there are several factors related to the combined use of psychotropic medication that may influence the perspective-taking ability, namely the type of antidepressants (tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, monoamine oxidase inhibitors, and other antidepressants) and benzodiazepines (short-acting or long-acting), the dose of each drug, and the percentage of days of concomitant drug use. However, we were not able to test these variables as potential moderators of any concomitant drug use effects observed, due to the small sample of the present study. The literature in the present field is still very limited and multi-center studies pursuing the influence that long-term use of benzodiazepines and antidepressants may have on social cognition, including perspective-taking ability, are needed.

Contrary to our hypothesis, the modulation of N170 and LPPs components was present in the group of concomitant benzodiazepines and antidepressants users. Overall, the results seem to indicate that long-term use of these psychotropic substances together neither affect perspective taking abilities and neither the processing of related information. Although the evidences of deficits in several general cognitive abilities in long-term benzodiazepine users,[31,71] the combined use of benzodiazepines and antidepressants on long-term seems to preserve at least the perspective-taking ability of social cognition. However, we should bear in mind that the small sample of the study is a limitation when drawing conclusions. Additionally, the lack of previous studies with a similar sample, makes any interpretation difficult to support. Further research within this field conducted with a larger sample is necessary to strengthen the present finding. We hope, however, to have brought important evidence to light, which may help future research on social cognition under the influence of benzodiazepines and antidepressants.

Data availability

Underlying data

DANS: Psychotropic long-term use and perspective taking: behavioral and neural dataset, https://doi.org/10.17026/dans-xjs-kje4.

This project contains the following underlying data:

- Accuracy.xlsx
- LPPe_Congruent.xlsx
- LPPe_Incongruant.xlsx
- LPPI_Congruent.xlsx
- LPPI_Incongruent.xlsx
- N170_Congruent.xlsx
- N170_Incongruent.xlsx
- Reaction_times.xlsx
- Sociodemographic_neuropsychological.xlsx

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Version 2

Reviewer Report 14 November 2022

https://doi.org/10.5256/f1000research.139791.r155173

✔ **Helena Hartmann**
Clinical Neurosciences, Department of Neurology, University Hospital Essen, Essen, Germany

All my comments were answered and I am happy to approve this publication now.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Empathy, perspective taking / theory of mind, neuroimaging (fMRI), placebo analgesia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 30 August 2022

https://doi.org/10.5256/f1000research.135192.r146668

✘ **Helena Hartmann**
Clinical Neurosciences, Department of Neurology, University Hospital Essen, Essen, Germany

I am an expert on empathy (specifically in the domain of pain) and Theory of Mind, but don't have any experience with EEG.

Summary
In general, the main question of the present manuscript was to investigate whether the combined use of benzodiazepines and antidepressants affect perspective taking. In a between-subjects design, the authors compared users of both medication with controls on the behavioral and neural level (using event-related potentials) in a perspective-taking task. The groups did not differ in their task performance nor in their neural activity. The authors conclude that taking benzodiazepines and antidepressants together does not affect perspective-taking abilities.

Strengths
The research question is interesting and relevant, given that concomitant use of multiple medications is common and investigating this increases ecological validity (as compared to investigating effects of single medications alone). The manuscript is well structured and easy to follow. The methods are appropriately detailed, and allow for replication of the study. Results are clearly described and relevant statistics are reported. I appreciate that the authors openly shared their data. I also really like the last paragraph of the discussion, as it appropriately highlights limitations and caveats of the work.

I have significant reservations, as outlined below, which include many comments that need to be addressed, before I can recommend the article to be of sufficient quality. My comments are structured into major and minor, and as they appear in the text. I hope the authors find my suggestions helpful to improve the manuscript.

Major
The authors start their abstract and introduction talking about empathy and the different parts of empathy, however, the study investigated only a part of empathy, i.e., perspective taking. It might be misleading to speak of empathy generally, as researchers often also include the more emotional, affect sharing component under this term, as well as concern/sympathy. For example, the first sentence of the abstract talks about results regarding empathic pain, which relates more to affect sharing and not to perspective taking. The abstract and introduction should clearly state what exact concepts are being investigated here and introduce them adequately to avoid misunderstandings. For example, the authors could make a case that affective empathy has been researched a lot in regard to medication interactions, while this is less the case for cognitive empathy?

Why were the scores of the cognitive tests included in a single analysis left raw and not standardized (in order to better compare the beta values between the measures)?

The authors mention that “Scores of cognitive tests (raw scores) in which differences between groups were detected were entered as main predictors of behavioral measures and N170, and LPPs modulation (independent models).” However, this violates the assumption of independence of covariate and treatment effect (see Field *et al.*, 2012, p. 465-466, who states: “when treatment groups differ on the covariate, putting the covariate into the analysis will not ‘control for’ or ‘balance out’ (...) differences (Lord, 1967, 1969)”).[1,2,3] According to his argument, only covariates where the groups do not differ on can be used as covariates.

Furthermore, why were the regressions run separately for the two groups and how do the authors explain effects in the control but not the experimental group?

Why do the authors not follow up on the significant emotion x group interaction in the accuracy ANOVA? If I am not mistaken, this interaction hints at a group effect specific to some emotions and independent of congruency? It might be interesting to follow up on, even if the authors did not have specific hypotheses on this effect.

As the authors report null findings regarding effects of concomitant use of benzodiazepines and antidepressants on perspective taking, I urge them to redo their analyses using a Bayesian framework (e.g. in JASP, https://jasp-stats.org/, which is similarly straightforward as SPSS). This would give the reader an indication of the relative evidence for the null compared to alternative hypothesis, especially also considering the rather low sample size. This would make the authors' conclusion that "the combined use of benzodiazepines and antidepressants on long-term seem to preserve at least the perspective-taking ability of social cognition" much stronger.

It sounds to me like the ROIs for the ERP analysis were not chosen independently, but based on the data that they collected (e.g. Button, 2019), but then also affirmed with previous literature. Could the authors comment on this?[4]

Results, Behavioral Results: How do the authors explain that the LPPe/LPPl were higher for congruent vs. incongruent conditions, when previous studies found the opposite (as stated in the introduction)? Also, I am a bit confused by those results as the authors also found an interaction between emotion and congruency in both LPPe and LPPl. In that case, the main effect of congruency should not be interpreted and plotted in Fig. 2, but instead the interaction? I think there is a typo in the paragraph about the LPPI as the authors still talk about LPPe there in the second to last sentence.

Why was reaction time also analyzed? Is this measure also related to perspective taking? What hypotheses did the authors have here?

One important point for me is whether the task actually measured perspective taking. From what I understood, you measured accuracy rates (and reaction times), so not how good participants were necessarily in finding out the emotion of the masked person, but how good they were in matching the emotion they thought fitted with an emotion they see in a picture afterwards. This to me sounds more like emotion identification. I would appreciate a discussion of the limitations of this task in the discussion.

Discussion: Why is the meta analysis mentioned at all if it is "methodologically far" from the present study? Does it help to interpret the findings of this study in any way?

In general, the few significant results that the study finds are not discussed at all in light of current literature but just mentioned as being "unexpected". A more throrough discussion of what these results could mean is warranted.

Minor

Introduction, Paragraph 2: The last part of the first sentence (starting with "Perspective-taking enables us…") reads a bit grammatically wrong – please recheck (maybe another "– " after "Theory of Mind"?

Introduction, Paragraph 2: Please revise the sentence "The ability to take the perspective of

another person is known as emotional perspective-taking and is determinant for the success of social interactions". This is not necessarily true, because taking the perspective of another person is also a cognitive process and does not need to be emotional. Maybe the authors mean "The ability to understand the emotions of another person is ..."?

Introduction, Paragraph 3: How was the oxazepam study on emotional mimicry? In the sentence later the authors specify that that study measured empathy for pain, which is typically "affect sharing". Please revise so this becomes a bit clearer.

Introduction, Paragraph 3: I would appreciate some statistics/numbers on the concomitant use of benzodiazepines and antidepressants compared to single use of either, so that the context for and necessity of the study is set better.

Introduction, Paragraph 7: Are the "neurocognitive" measures the same as the "neuropsychological" measures mentioned in the methods?

Just an idea: The authors could also make a case in the introduction that investigating the concomitant use of the medications is ecologically more valid as this better reflects real medication use, as opposed to taking a single medication? (if there is evidence for that)?

Do the authors think that gender of the people in the video might have had an influence on the results? Were the stimuli for congruent and incongruent conditions balanced in terms of gender?

Methods, Participants: How many people in the experimental group were excluded based on having "psychiatric diagnosis aside from anxiety and depression"?

Methods, Procedures: "... were invited to participate IN a second session...."

Methods, Statistical analysis, Paragraph 2: "...were analyzed by a mixed ANOVA... with group as A between-subjects factor..."

Results: Please add the test statistics to Table 1. It might also be nice to report all full ANOVA results in the Supplement.

Results, Behavioral Results: "...were examined using A mixed factor ANOVA"

Discussion, Paragraph 2: "Bearing IN mind..."

Discussion, Paragraph 8: "...substances together neither affect ... nor the processing of related information."

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Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Empathy, perspective taking / theory of mind, neuroimaging (fMRI), placebo analgesia

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 12 Oct 2022

Ana Gonçalves

I have significant reservations, as outlined below, which include many comments that need to be addressed, before I can recommend the article to be of sufficient quality. My comments are structured into major and minor, and as they appear in the text. I hope the authors find my suggestions helpful to improve the manuscript.

R: We thank Helena Hartmann for the careful review of our manuscript and the important points raised below. We will comment on each point, tracking the corresponding changes that were made in the manuscript.

Major

The authors start their abstract and introduction talking about empathy and the different parts of empathy, however, the study investigated only a part of empathy, i.e., perspective taking. It might be misleading to speak of empathy generally, as researchers often also include the more emotional, affect sharing component under this term, as well as

concern/sympathy. For example, the first sentence of the abstract talks about results regarding empathic pain, which relates more to affect sharing and not to perspective taking. The abstract and introduction should clearly state what exact concepts are being investigated here and introduce them adequately to avoid misunderstandings. For example, the authors could make a case that affective empathy has been researched a lot in regard to medication interactions, while this is less the case for cognitive empathy?

R: We appreciate your suggestion. We added the following information to the abstract and introduction sections: (abstract) "(...) the perspective-taking facet of (...)"; (introduction, paragraph 4) "Thus, the effects of medication interactions used for long periods on the perspective-taking facet of empathy are still unknown."

In our opinion, the concept of perspective-taking is adequately introduced in the first paragraphs.

Why were the scores of the cognitive tests included in a single analysis left raw and not standardized (in order to better compare the beta values between the measures)?

R: In most situations, to test the difference between performance on two tasks, it is necessary to standardize the scores. However, when a subject's performance is compared with that of controls on the same task, under two different experimental conditions, the standardization is unnecessary, Crawford and Garthwaite (2005).

Crawford, J. R., & Garthwaite, P. H. (2005). Testing for Suspected Impairments and Dissociations in Single-Case Studies in Neuropsychology: Evaluation of Alternatives Using Monte Carlo Simulations and Revised Tests for Dissociations. Neuropsychology, 19(3), 318–331. https://doi.org/10.1037/0894-4105.19.3.318

The authors mention that "Scores of cognitive tests (raw scores) in which differences between groups were detected were entered as main predictors of behavioral measures and N170, and LPPs modulation (independent models)." However, this violates the assumption of independence of covariate and treatment effect (see Field et al., 2012, p. 465-466, who states: "when treatment groups differ on the covariate, putting the covariate into the analysis will not 'control for' or 'balance out' (...) differences (Lord, 1967, 1969)").1,2,3 According to his argument, only covariates where the groups do not differ on can be used as covariates.

R: This is a good point. We wanted to examine the association between neuropsychological functioning and behavioral/ERP components, regardless of the direction of the influence of the effects. The choice of multiple linear regression was only to allow entering multiple neuropsychological measures and to control for their covariance in a practical manner (an alternative would be to use partial correlations, but it is a less common form of analyzing data in this field and are mathematically equivalent to the regression models employed). Note that this was not the main analysis of the study, and was intended to verify if the differences that we detected in neuropsychological functioning could account for the behavioral/ERP results in the experimental group.

We know that it is a bad idea to adjust for covariates when we suspect these covariates could have been affected by the treatment, however we were less cautious here because the analyses were run separately for the experimental and control group.

Furthermore, why were the regressions run separately for the two groups and how do the authors explain effects in the control but not the experimental group?

R: The regression was first computed only for the experimental group since it was our group of interest. To further explore and clarify the results, the analysis was extended to the control group. This information was added to the methods section (statistical analysis, paragraph 3).
Regarding the effects in the control group but not the experimental, it is now addressed in the discussion: "Furthermore, a meta-analysis examining the boundary conditions of threat-related attentional biases in anxiety showed that a significant bias also occurred with stimuli outside awareness. Additionally, the bias is present in different types of anxious populations, including nonclinical individuals, and is not observed in non anxious individuals. This attentional bias in anxious individuals may account for higher accuracy rates when identifying emotional situations. However, our results showed accuracy rates predicted by anxiety and psychopathological symptomatology only in control subjects and regarding happiness scenarios. Here we should consider that ceiling effects could have account for these results. In fact, ceiling effects have been known to hinder solid interpretations of the results, especially for facial expressions of happiness."

Why do the authors not follow up on the significant emotion x group interaction in the accuracy ANOVA? If I am not mistaken, this interaction hints at a group effect specific to some emotions and independent of congruency? It might be interesting to follow up on, even if the authors did not have specific hypotheses on this effect.

R: Although we found a significant emotion x group interaction, none of the post-hoc comparisons achieved significance (all p >.066). This information was added to the results section.

As the authors report null findings regarding effects of concomitant use of benzodiazepines and antidepressants on perspective taking, I urge them to redo their analyses using a Bayesian framework (e.g. in JASP, https://jasp-stats.org/, which is similarly straightforward as SPSS). This would give the reader an indication of the relative evidence for the null compared to alternative hypothesis, especially also considering the rather low sample size. This would make the authors' conclusion that "the combined use of benzodiazepines and antidepressants on long-term seem to preserve at least the perspective-taking ability of social cognition" much stronger.

R: We appreciate your suggestion for an alternative analysis which we will consider in future work. A Bayesian framework could provide additional information, but the choice of the present analysis allowed us to compare the performance between groups as we intended. We have now emphasized the limitation of having a low sample size in the

discussion. The present form is (discussion, last paragraph): "However, we should bear in mind that the small sample of the study is a limitation when drawing conclusions. Additionally, the lack of previous studies with a similar sample, makes any interpretation difficult to support. Further research within this field conducted with a larger sample is necessary to strengthen the present finding. We hope, however, to have brought important evidence to light, which may help future research on social cognition under the influence of benzodiazepines and antidepressants."

It sounds to me like the ROIs for the ERP analysis were not chosen independently, but based on the data that they collected (e.g. Button, 2019), but then also affirmed with previous literature. Could the authors comment on this?[4]

R: The ROIs for the ERP analysis were chosen based on visual inspection of ERP grand-average and topographical maps of our EEG records. These results were in accordance with previous studies and led us to set the specified ROIs. This is a common procedure in this field.

Results, Behavioral Results: How do the authors explain that the LPPe/LPPl were higher for congruent vs. incongruent conditions, when previous studies found the opposite (as stated in the introduction)? Also, I am a bit confused by those results as the authors also found an interaction between emotion and congruency in both LPPe and LPPl. In that case, the main effect of congruency should not be interpreted and plotted in Fig. 2, but instead the interaction? I think there is a typo in the paragraph about the LPPI as the authors still talk about LPPe there in the second to last sentence.

R: Previous studies that reported higher LPP amplitudes elicited by incongruent trials used tasks requiring an evaluative congruity between primes and facial or verbal targets, whereas our task required attending the scenes, inferring the mental state of the masked interveners, and deciding if the FEE displayed after the scene matched the one previously inferred. The recognition of the masked person's emotion in the stimuli displayed by the target FEE in our task may explain the increased amplitudes to congruent stimuli since the LPP is also modulated by the explicit recognition of stimuli, exhibiting larger amplitudes in response to recognized stimuli vs. new (discussion, paragraph 6).

In our opinion, such plots representing the emotion x congruency interaction will be hard to interpret given the large amount of information represented.

There was a typo in the paragraph about LPPl. LPPe was changed to LPPl: "Pairwise comparisons revealed that congruent conditions elicited higher LPPl amplitudes than incongruent conditions (p = .002) (Fig. 2)."

Why was reaction time also analyzed? Is this measure also related to perspective taking? What hypotheses did the authors have here?

R: We appreciate this comment. Previous studies (Abramowitz et al., 2014; Smith et al., 2014) found that schizophrenia outpatients showed poorer performance and took significantly

longer to complete an emotional perspective-taking task than healthy controls. In our study, we analyzed reaction times because we expected worst performance of the experimental group on the perspective-taking task and longer reaction times could be observed. We added this information to introduction (last paragraph): "Furthermore, considering that it was previously found that subjects from a clinical sample took longer to complete an emotional perspective-taking task, besides showing poorer performance than healthy controls[35,36], we analyzed reaction times to clarify if they were affected in our study."

A.C. Abramowitz, E.J. Ginger, J.K. Gollan, M.J. Smith. Empathy, depressive symptoms, and social functioning among individuals with schizophrenia. Psychiatry Res., 216 (2014), pp. 325-332

M.J. Smith, W.P. Horan, D.J. Cobra, T.M. Karpouzian, J.M. Fox, J.L. Reilly, *et al.* Performance-based empathy mediates the influence of working memory on social competence in schizophrenia. Schizophr. Bull., 40 (2014), pp. 824-834

One important point for me is whether the task actually measured perspective taking. From what I understood, you measured accuracy rates (and reaction times), so not how good participants were necessarily in finding out the emotion of the masked person, but how good they were in matching the emotion they thought fitted with an emotion they see in a picture afterwards. This to me sounds more like emotion identification. I would appreciate a discussion of the limitations of this task in the discussion.

R: This is an interesting issue. The current experimental design was based on previous studies assessing contextual congruency (Diéguez-Risco, Aguado, Albert, & Hinojosa, 2013), defined here as the matching between a target emotion portrayed in a facial expression and the emotion portrayed by the previous scenario. However, distinct from previous studies, an accurate decision in our task requires an accurate inference of the emotional state of the masked intervener. We instructed participants to attend the scenes, infer the mental state of the masked interveners, and decide if the FEE displayed after the scene matched the one previously inferred. Thus, with this experimental manipulation, we investigated perspective-taking abilities through the behavioral performance (see introduction, paragraph 4; methods, emotional perspective-taking task, paragraph 1; discussion, paragraph 6).

Discussion: Why is the meta analysis mentioned at all if it is "methodologically far" from the present study? Does it help to interpret the findings of this study in any way?

R: The meta-analysis assessed the effects of benzodiazepines administration on the ability of identifying facial expressions of emotion (FEE), an ability required in the task of the present study. The meta-analytic results could help to interpret any effects observed of the concomitant use of benzodiazepines and antidepressants on the perspective-taking ability.

In general, the few significant results that the study finds are not discussed at all in light of current literature but just mentioned as being "unexpected". A more throrough discussion of what these results could mean is warranted.

R: We appreciate this comment that will considerably improve the work. This issue is now addressed in the discussion: "Furthermore, a meta-analysis examining the boundary conditions of threat-related attentional biases in anxiety showed that a significant bias also occurred with stimuli outside awareness. Additionally, the bias is present in different types of anxious populations, including nonclinical individuals, and is not observed in non anxious individuals. This attentional bias in anxious individuals may account for higher accuracy rates when identifying emotional situations. However, our results showed accuracy rates predicted by anxiety and psychopathological symptomatology only in control subjects and regarding happiness scenarios. Here we should consider that ceiling effects could have account for these results. In fact, ceiling effects have been known to hinder solid interpretations of the results, especially for facial expressions of happiness."

Minor

Introduction, Paragraph 2: The last part of the first sentence (starting with "Perspective-taking enables us…") reads a bit grammatically wrong – please recheck (maybe another "– " after "Theory of Mind"?

R: We added another "-" to the text.

Introduction, Paragraph 2: Please revise the sentence "The ability to take the perspective of another person is known as emotional perspective-taking and is determinant for the success of social interactions". This is not necessarily true, because taking the perspective of another person is also a cognitive process and does not need to be emotional. Maybe the authors mean "The ability to understand the emotions of another person is …"?

R: This is an interesting issue. We followed the definition of emotional perspective-taking of Derntl and colleagues (2009) but we agree that taking the perspective of another person is also a cognitive process. The present form of the above-mentioned sentence is: "The ability to correctly infer the emotional states of another person is known as emotional perspective-taking and is determinant for the success of social interactions."

Introduction, Paragraph 3: How was the oxazepam study on emotional mimicry? In the sentence later the authors specify that that study measured empathy for pain, which is typically "affect sharing". Please revise so this becomes a bit clearer.

R: The study of Nilsonne and colleagues investigated the effects of oxazepam on emotional mimicry and empathic responding using two experiments. The empathy experiment investigated the effects of oxazepam by pain stimulating the participant and a confederate. The emotional mimicry experiment was deleted from the sentence to make it clearer (introduction, paragraph 3): "(…) investigated the effects of oxazepam on empathic responding."

Introduction, Paragraph 3: I would appreciate some statistics/numbers on the concomitant use of benzodiazepines and antidepressants compared to single use of either, so that the context for and necessity of the study is set better.

R: The main goal of the present study was based on the real and current context of benzodiazepines (BZDs) being often additionally administered to antidepressants (ADs), to manage anxiety or insomnia in patients with depression, since ADs have minimal therapeutic effects during the initial weeks of administration. The decision to investigate the combined use of these drugs is due to knowledge of the current context from clinical practice of some team members. The numbers for this practice of combined prescription in the USA are reported in Bushnell *et al.* (2017): "one in 10 patients who initiated ADs concomitantly initiated BZDs in the USA. However, BZDs are sometimes continued for longer periods than intended in real-world clinical practice, possibly owing to their dependency—one study found that approximately 12% of patients who received concomitant BZD and AD therapy (AD+BZD) continued long-term BZD use."

In our opinion, the context and necessity of the study is now better set out although we did not mention statistics/numbers (introduction, last paragraph): "It is common to prescribe benzodiazepines and antidepressants simultaneously in initial depression treatment, however it has been previously reported that the simultaneous use extends beyond the initial period and becomes long term."

Bushnell G, Sturmer T, Gaynes B, Pate V, Miller M. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001-2014. JAMA Psychiatry. 2017;74(7):747–55.

Introduction, Paragraph 7: Are the "neurocognitive" measures the same as the "neuropsychological" measures mentioned in the methods?

R: The neurocognitive measures are the same neuropsychological measures listed in the methods section.

Just an idea: The authors could also make a case in the introduction that investigating the concomitant use of the medications is ecologically more valid as this better reflects real medication use, as opposed to taking a single medication? (if there is evidence for that)?

R: We appreciate this comment. We added information in line with your suggestion (introduction, last paragraph): "It is common to prescribe benzodiazepines and antidepressants simultaneously in initial depression treatment, however it has been previously reported that the simultaneous use extends beyond the initial period and becomes long term."

Do the authors think that gender of the people in the video might have had an influence on the results? Were the stimuli for congruent and incongruent conditions balanced in terms of gender?

R: This is a good point. The FEE was selected from the NimStim Face Stimulus Set, picking the five most accurately identified facial expressions for each emotional category which led to 30 female and 30 male facial stimuli. These stimuli were balanced in terms of gender for

congruent and incongruent conditions (15 female and 15 male for both conditions). In our opinion, it is unlikely that the gender of actors in the stimuli might have influenced the results, since the stimuli were balanced for both conditions and the set was the same for the two groups (only the order of stimuli presentation changed between participants in a random way).

Methods, Participants: How many people in the experimental group were excluded based on having "psychiatric diagnosis aside from anxiety and depression"?

R: Two participants were excluded based on that criteria but I considered them in the number of participants excluded by taking psychotropic medication besides benzodiazepines and antidepressants. This was changed accordingly in the text.

Methods, Procedures: "... were invited to participate IN a second session...."

R: It was a typo and was corrected to "...in a second session...".

Methods, Statistical analysis, Paragraph 2: "...were analyzed by a mixed ANOVA... with group as A between-subjects factor..."

R: "a" was deleted.

Results: Please add the test statistics to Table 1. It might also be nice to report all full ANOVA results in the Supplement.

R: The tests statistics were added to Table 1.

Results, Behavioral Results: "...were examined using A mixed factor ANOVA"

R: "a" was added before "mixed factors ANOVA".

Discussion, Paragraph 2: "Bearing IN mind..."

R: It was a typo and was corrected to "...in mind...".

Discussion, Paragraph 8: "...substances together neither affect ... nor the processing of related information."

R: The sentence was changed to "...substances together neither affect ... nor the processing of related information."

Competing Interests: No competing interests.

Reviewer Response 11 Nov 2022

Helena Hartmann

I want to thank the authors for their replies to all of my comments and for a successful revision. All of my comments were addressed and I have no further questions :)

Competing Interests: No competing interests were disclosed.