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Early View

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Experimental social rejection increases dyspnoea perception and neural processing of respiratory sensations in healthy subjects

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Experimental social rejection increases dyspnoea perception and neural processing of respiratory sensations in healthy subjects

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"Take home" message:

Social rejection is associated with increased dyspnoea perception and neural processing of respiratory sensations.

Patients suffering from dyspnoea frequently report social rejection as a severe limitation of their lives[1]. While the effects of different social challenges on the respiratory system are already established in animal models[2,3], little is known about potential consequences of social rejection on the perception and neural processing of dyspnoea in humans. Detrimental effects of social rejection are well documented for other aversive somatic symptoms[4,5]. The current study examined whether social rejection would increase perceived dyspnoea and whether this would be paralleled by increased neural processing of respiratory sensations as measured with respiratory-related evoked potentials (RREPs) in the electroencephalogram (EEG).

39 healthy females (age median(range) in years: 19.00(18.00-41.00)) took part in this study after providing written consent (ethical approval by the University of Leuven ethics committee: G-2016-10-646). Each participant underwent a rejection, inclusion and control condition in a counterbalanced order (Figure 1A). The rejection and inclusion conditions were created using the well-validated and clinically reliable[6,7] Cyberball paradigm[7](Figure 1B). Cyberball is a virtual ball-tossing game in which participants believe to play a ball game with two other real players. In reality, no other players exist, and participants are playing a computer-generated game. During inclusion, participants receive the ball for ≈33% while during rejection participants receive the ball only for ≈6%. The effectiveness of the Cyberball manipulation was assessed by three ratings[7] on feeling accepted-rejected (1=accepted to 9=rejected), received ball throws (0-100%) and a mood scale with lower values representing more negative mood. The control condition, which served as a baseline including no social component, was created using another virtual ball-tossing game that explicitly stated that no other players are involved (Figure 1C). Each condition consisted of two consecutive blocks containing 30 ball throws each (≈3minutes).

Each block was followed by a 3-minute dyspnoea phase during which an individually tailored strong level of dyspnoea was induced by inspiratory resistive loads. This dyspnoea level was individually predetermined prior to the experimental phase by presenting different inspiratory resistive load magnitudes repeatedly until a subjective level of strong dyspnoea intensity was reached (="5" on modified Borg scale; mean$\pm$SD: 27.41$\pm$13.23cmH$_2$O/L/s). Simultaneously, in the dyspnoea phase, RREPs were evoked by applying inspiratory occlusions (150ms) randomly to every second to fifth inspiration while EEG was recorded continuously. During

the dyspnoea phase, participants were breathing through a breathing circuit via a mouthpiece while wearing a nose-clip. The circuit consisted of a two-way non-rebreathing valve with the inspiratory port connected to a pneumotachograph and a loading manifold, to administer the inspiratory resistive loads (all Hans Rudolph Inc., Shawnee, USA), and an occlusion device (Aspire Products, Gainesville, USA) used to trigger the inspiratory occlusions[8]. Respiratory variables including breathing frequency (f), inspiratory time (T_I), tidal volume (V_T), mean airflow (V') and peak inspiratory mouth pressure (P_{Imax}) were calculated based on the continuously recorded mouth pressure and airflow signals. After each dyspnoea phase ratings of dyspnoea intensity, unpleasantness and threat were obtained using visual analogue scales (0=not noticeable/not unpleasant/not threatening to 100=maximally imaginable intensity/unpleasantness/threat).

129-channel EEG (Philips EGI, Eugene, USA) was recorded at 250Hz during each dyspnoea phase (reference: Cz). The later RREP components P2 and P3 (>150ms post-occlusion) were analysed as they represent cognitive higher-order neural processing of respiratory sensations[9] and are susceptible to social modulations.

Statistical analyses were conducted using SPSS 24 (IBM Corp., Armonk, USA). Ratings, respiratory variables and P2/P3 amplitudes were averaged across the two blocks of each condition. Ratings of the Cyberball manipulation check were analysed using dependent t-tests/Wilcoxon signed-rank tests. To investigate the pure rejection and inclusion effects on the respiratory variables and the main outcomes of interest (dyspnoea ratings, P2/P3), difference scores were calculated for the rejection (Δrejection=rejection-minus-control) and inclusion condition (Δinclusion=inclusion-minus-control). Respiratory variables and dyspnoea ratings were compared with dependent t-tests/Wilcoxon signed-rank tests (Δrejection vs. Δinclusion). P2 and P3 mean amplitudes were analysed via ANOVAs with the within-factors condition (Δrejection/Δinclusion) and brain hemisphere (left/right). Interaction effects were followed up using dependent t-tests (Δrejection vs. Δinclusion per hemisphere). The significance level was p<.05 unless corrected for multiple comparisons using the modified False Discovery Rate[10].

All ratings of the Cyberball manipulation check (corrected: p<.024) differed significantly (all p's<.001) confirming a successful induction of social rejection and inclusion. For rejection,

higher rejection (rejection median(range): 7.50(3.00-8.00); inclusion mean$\pm$SD: 3.22$\pm$1.57), fewer ball throws (rejection mean$\pm$SD: 7.28$\pm$3.84; inclusion median(range): 31.00(18.50-55.00)) and more negative mood (rejection mean$\pm$SD: 5.01$\pm$1.21; inclusion mean$\pm$SD: 5.91$\pm$1.05) were reported.

No difference between Δrejection and Δinclusion was found on any respiratory variable (all p's>.20). The respective values for rejection, inclusion and control conditions were for f in breaths/min (means$\pm$SDs) 13.01$\pm$4.32, 13.10$\pm$5.40, 12.62$\pm$4.66; for T_I in s (means$\pm$SDs) 2.80$\pm$0.99, 2.94$\pm$1.14, 2.98$\pm$1.21; for V_T in L (median(range)) 0.54(0.36-1.29), 0.58(0.36-1.22), 0.58(0.33-1.27); for V' in L/s (means$\pm$SDs) 0.22$\pm$0.07, 0.22$\pm$0.06, 0.22$\pm$0.07 and for P_{Imax} in cmH$_2$O (means$\pm$SDs) -10.33$\pm$4.72, -10.30$\pm$4.90, -10.23$\pm$4.78.

A significant difference (corrected: p<.027) was found between Δrejection and Δinclusion conditions for dyspnoea intensity (p=.01) and unpleasantness (p=.005) with higher ratings for Δrejection compared to Δinclusion. A similar trend was found for dyspnoea threat (p=.07) (Figure 1D). Overall, the dyspnoea ratings confirm a successful dyspnoea induction for rejection, inclusion and control conditions with respective values in means$\pm$SDs (intensity: 52.67$\pm$19.04, 47.05$\pm$17.44, 48.82$\pm$19.81; unpleasantness: 55.60$\pm$21.45, 47.54$\pm$19.55, 49.74$\pm$20.17; threat: 37.28$\pm$25.06, 31.88$\pm$20.55, 34.27$\pm$24.43).

For the P2 a significant main effect was found for the factor condition (p=0.04) with higher mean amplitudes for Δrejection compared to Δinclusion. For the P3 a significant interaction effect for the factor condition and hemisphere was found (p=0.01). The follow-up tests (corrected: p<.033) revealed a significant difference between both conditions for the left (p=.016), but not the right hemisphere (p=.80) with larger mean amplitudes for Δrejection compared to Δinclusion (Figure 1E, 1F).

The present findings demonstrate increased dyspnoea intensity and unpleasantness after social rejection compared to inclusion with a similar trend for dyspnoea threat. Consistent with the ratings, larger amplitudes for RREP components P2 and P3 were found after rejection compared to inclusion while respiratory variables showed no differences. Together, the current findings indicate that social rejection increases perceived dyspnoea and the neural processing of respiratory sensations in the absence of respiratory changes.

These findings are in line with previous studies demonstrating aversive effects of rejection on breathing in animals[2,3] and on other somatic symptoms in humans[4,5]. For example, Bernstein and Claypool[4] showed higher pressure pain sensitivity after rejection compared to inclusion using the same Cyberball paradigm. Similarly, Canaipa et al.[5] found increased electrical pain reports after rejection compared to inclusion. Notably, overlapping brain areas including the insula and dorsal anterior cingulate cortex are activated during the experience of rejection[11] and dyspnoea[12]. This might suggest a potential underlying brain mechanism by which rejection could potentiate the perception of dyspnoea. However, literature also exists which challenges the prediction of overlapping brain areas[13]. Therefore, future neuroimaging studies are required to further investigate this hypothesis and to substantiate potential hemispherical differences herein.

The current findings might have an important clinical implication. Social rejection is a severe problem in dyspnoeic patients[1] and might be a contributing factor to the worsening of dyspnoea. However, dyspnoea and the resulting social rejection are frequently overlooked by healthcare professionals which might further contribute to its aggravation[14]. Therefore, social rejection should be recognized by clinicians and specifically targeted in the treatment of dyspnoeic patients to break the vicious cycle of dyspnoea-social rejection-dyspnoea. For example, a cost-effective strategy could be Internet-based technologies to implement online group-activities/support into the lives of dyspnoeic patients to reduce their social rejection[15].

Certain limitations of this study are noteworthy. This study was conducted in healthy females which were mainly psychology students. This limits the generalization to dyspnoeic patient and male populations, particularly because females might react stronger to social rejection than males[16]. Additionally, the ratings of the Cyberball manipulation check might have in itself potentiated the social rejection/inclusion manipulation. Furthermore, additional dyspnoea induction methods (e.g., CO_2 inhalation, exercise-induced dyspnoea, vicarious dyspnoea[17]) should be applied to allow the investigation of other dyspnoea qualities (e.g., chest tightness or air hunger). The present study only investigated the effects of brief social rejection. Thus, future studies should investigate the effects of repeated or long-term social rejection.

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Figure Legend

Figure 1. **A)** Schematic representation of the experimental phase for one exemplary participant. The Cyberball manipulation check included ratings on feeling accepted-rejected (1=accepted to 9=rejected), received ball throws from other players (0-100%) and a mood scale with lower values representing more negative mood.

B) Schematic representation of the Cyberball game used to create the rejection and inclusion condition. Dotted arrows indicate all possible trajectories of the ball.

C) Schematic representation of the ball-tossing game used to create the control condition. During this game, participants observed a ball moving vertically up/down the screen. Whenever the ball diverted from this trajectory and landed in a left/right square, participants had to indicate this via button press. Dotted arrows indicate all possible trajectories of the ball.

D) Mean (SE) for the change in dyspnoea ratings including intensity, unpleasantness and threat for the rejection (Δrejection=rejection-minus-control) compared to the inclusion condition (Δinclusion=inclusion-minus-control). Positive values indicate higher and negative values lower dyspnoea intensity, unpleasantness and threat. *: $p<.05$. **: $p<.01$. #: $p=.07$.

E) Grand average waveform of the respiratory-related evoked potential (RREP) for the rejection, inclusion and control condition with corresponding P2 and P3 topographies. Data were processed offline using BESA Research 6.0 (BESA GmbH, Gräfelfing, Germany). Data were filtered (high-pass: 0.1Hz, low-pass: 30Hz, notch: 50Hz), artefact corrected and average re-referenced. Epochs 200ms before and 1000ms after occlusion onset were extracted and averaged. Based on previous research[9], P2 and P3 were identified as positive subject-specific peaks in the latency around 160–230ms after occlusion onset for the P2 and in the latency around 250-350ms after occlusion onset for the P3. Mean amplitudes for P2 and P3 were then calculated by averaging the signal in a latency window around these subject-specific peaks (P2: ±20ms; P3: ±30ms) across the respective electrodes (P2-left hemisphere: 29/30/36; P2-right hemisphere: 104/105/111; P3-left hemisphere: 7/30/31; P3-right hemisphere: 80/105/106).

F) Mean (SE) for the change in mean amplitude (μV) of P2 and P3 for the rejection (Δrejection=rejection-minus-control) compared to the inclusion condition (Δinclusion=inclusion-minus-control) across both brain hemispheres (top) and for left/right hemispheres separately (bottom). No significant differences were found for the earlier RREP components Nf, P1 and N1 which represent more sensory first-order neural processing of respiratory sensations[9](all p's>.063). *: $p<.05$.

Contributors

AvL, OVdB, IVD, MV, JS and MH conceptualized the research design and research protocol. MH and MV were responsible for the data collection. MH and AvL were responsible for the statistical analysis. MH and AvL had access to all the data in the study and take responsibility for the integrity of the data as well as the data analysis. MH created the figure. MH wrote the manuscript. MH, JS, MV, IVD, OVdB and AvL provided feedback on the protocol, interpretation of the study results and on the manuscript. All authors read and approved the final version.

Declaration of interests

Disclosures can be found alongside this article at erj.ersjournals.com

A) Cyberball manipulation check | Cyberball manipulation check

Rejection | Dyspnoea & Occlusions | Rejection | Dyspnoea & Occlusions | Control | Dyspnoea & Occlusions | Control | Dyspnoea & Occlusions | Inclusion | Dyspnoea & Occlusions | Inclusion | Dyspnoea & Occlusions

Dyspnoea ratings on dimensions intensity, unpleasantness and threat via visual analogue scales

B) Other players

Participant

C)

D) ΔDyspnoea Ratings

Change in dyspnoea

Intensity * | Unpleasantness ** | Threat #

Rejection | Inclusion

E) RREP

Rejection | Inclusion | Control

Amplitude (μV)

P2 | P3

Time (ms)

Rejection | Inclusion | Control

P2

P3

-2 μV

2 μV

F) ΔP2

Change in amplitude (μV)

*

ΔP3

Change in amplitude (μV)

Left * | Right

Rejection | Inclusion