Loneliness in the Brain: Distinguishing Between Hypersensitivity and Hyperalertness

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Please note that this report describes two studies. The first study has been conducted already to provide more precise predictions for the second study. This report is intended to pre-registered the predictions for the second study.

Abstract

Introduction: Loneliness has emerged as a pressing public health issue, necessitating greater understanding of its mechanisms to devise effective treatments. While the link between loneliness and biased social cognition is a commonly proposed, the precise nature of this relationship remains unclear. This study aims to investigate the cognitive processes underlying loneliness, specifically distinguishing between hypersensitivity (heightened initial response) and hyperalertness (slow habituation) to social stimuli in lonely individuals.

Methods: In Study 1, 36 participants were tested to identify the relevant EEG channels and time windows that show differential processing of angry vs happy faces and first vs later exposure in a roving oddball paradigm. Study 2 will compare these face processing effects in lonely and non-lonely participants. We aim to recruit a sample of 50 lonely and 50 non-lonely participants, who will be identified by their responses on a standardised loneliness questionnaire with population norms.

Results: In Study 1, a greater response to angry compared to happy facial expressions was observed between 120-170ms over posterior and central channels, and between 360 and 470ms over right posterior channels. A greater response to the initial compared to the fifth presentation of an emotional face was found between 480 and 600ms over right posterior and central channels. These findings align with previous research on emotion and novelty processing in similar experiments.
For Study 2, we anticipate observing higher response amplitudes when comparing angry expressions to happy expressions in lonely participants, indicating hypersensitivity. Furthermore, we expect to see greater amplitudes when comparing early presentations to late presentations of angry faces in lonely individuals, indicating increased alertness.

Discussion:

Keywords: loneliness, perceived social isolation, hypersensitivity, hyperalertness, event-related potentials, roving oddball, N170, N400, Late Positive Potential.

1. Introduction

Loneliness impacts up to 30% of the population, posing a significant public health challenge (Joint Research Centre of the European Union 2021; HM Government 2018). Loneliness differs from an individual's objective social connections. Instead, people experience loneliness when the perceived number or quality of their social relations is lower than they desire (Perlman and Peplau 1981). In recent years, studies have demonstrated that loneliness is a major psychosocial determinant of health. The health implications of loneliness are profound. It links to various health concerns like increased stress, immune system dysfunction, suicidal tendencies, cognitive decline, and even dementia, escalating morbidity and mortality rates (Holt-Lunstad et al. 2015; Heinrich and Gullone 2006). To tackle the harmful effects of loneliness, it's crucial to grasp its root causes or maintaining factors and develop effective solutions. While simply increasing opportunities for social interactions, termed "social prescribing", has not proven very effective, cognitive approaches seem more promising (Masi et al. 2011). Yet, the cognitive mechanisms behind loneliness are still not well understood. As a result, studying these underlying processes has become a primary focus in recent research.

The most prominent cognitive account of loneliness is the social evolutionary framework. One assumption of the social evolutionary framework (Hawkley and Cacioppo 2010; Hawkley and Capitanio 2015) is that our brain is wired to trigger protective measures and increase social seeking when we are isolated. This leads lonely people to be hypersensitive to social stimuli, particularly to social threats. As a result they are more prone to feeling anxious and more likely to withdraw from social scenarios to avoid harm (Meng et al. 2020). Supporting this, neurophysiological studies showed that lonely individuals tend to be more sensitive to negative social cues. For instance, an eye-tracking study in 85 young adults showed that lonely people spent longer looking at naturalistic scenes of social rejection (Bangee et al. 2014). Further, Cacioppo et al. (2009) investigated responses to social and non-social pictures with positive and negative valence from the International Affective Picture System in a sample of 23 university students with fMRI (J. T. Cacioppo et al. 2009). Lonely people showed greater BOLD response to social pictures in the visual cortex, which the authors interpret as an indication of greater visual attention to social stimuli in loneliness. Cacioppo and colleagues (2015) employed a Stroop task with social and non-social, positive and negative words together with EEG to investigate implicit attention in loneliness (S. Cacioppo, Balogh, and Cacioppo 2015). Their results indicated that lonely individuals distinguish between negative social and non-social words 200ms earlier than non-lonely individuals, suggesting an implicit attentional bias to negative social information. In a similar study, Cacioppo et al. (2016) found that lonely people distinguished between threatening and non-threatening stimuli 200ms earlier, suggesting an implicit attentional bias to threat in loneliness (S. Cacioppo et al. 2016). Grennan et al. (2021) investigated neural and behavioural responses in a target detection task with emotional facial expressions in 147 adults (Grennan et al. 2021). Loneliness was associated with slower responses when angry facial expressions were shown, indicating increased attentional capture by angry facial expression. This was accompanied by greater EEG source activity in the theta band in the left temporal cortex, which the authors link to stronger implicit biases during evaluation of social interactions (Schiller et al. 2019). Most recently, Du et al. employed a category judgement task with positive, negative, and neutral social and non-social stimuli in combination with EEG in 30 participants (Du et al. 2022). Their results indicated faster behavioural responses, a shorter N170 latency, and an enhanced P1 amplitude for negative social stimuli in lonely people. Together, these studies suggest that loneliness is indeed associated with hypersensitivity to social threats.

Within the social evolutionary framework, an alternative interpretation suggests that loneliness may not necessarily heighten sensitivity to social threats. Instead, it may impair an individual's ability to habituate to these threats. This concept aligns with recent theoretical developments in stress adaptation, emphasizing the importance of individual responses to repeated stressors (Quadt et al. 2020; A. Peters, McEwen, and Friston 2017). The habituation effect, a fundamental neurological process, entails a decreased response to stimuli that may initially appear threatening but do not lead to any harm over repeated exposures. While the literature on habituation effects in loneliness is comparatively sparse, several recent reports in loneliness and related conditions suggest that habituation may be an important mechanism. For instance, Morr and colleagues (2022) found that lonely men displayed reduced habituation in amygdala reactivity to threatening faces during the extinction phase of a conditioning paradigm with fMRI. Similarly, Berhe et al. (2023) reported reduced amygdala habituation to repeated presentations of threatening faces in a sample at risk for anxiety and depression and high levels of loneliness. This reduced amygdala habituation was associated with more negative evaluations of social interactions and a preference for being alone (Berhe et al. 2023). Furthermore, loneliness appears to alter stress reactivity, as governed by the hypothalamus-pituitary-adrenal (HPA) axis. This system, typically regulated by a negative feedback loop involving cortisol, seems disrupted in lonely individuals, leading to sustained high stress reactivity (Vitale and Smith 2022). Evidence includes persistently elevated cortisol levels, lower cortisol reactivity, and disrupted diurnal cortisol release rhythms (J. T. Cacioppo et al. 2000; Doane and Adam 2010). Collectively, these findings suggest that loneliness may be associated with reduced habituation to repeated stressors.

Current studies cannot distinguish between the hypersensitivity and hyperalertness accounts because of the set up of their experimental designs. To our knowledge, all published studies exploring the effects of loneliness on social perception employed stimuli that were presented in random order, intermixing positive and negative stimuli (Grennan et al. 2021; S. Cacioppo, Balogh, and Cacioppo 2015; Du et al. 2022). Larger responses to aversive stimuli in lonely people are generally interpreted as evidence of an attentional bias. Indeed, higher averaged responses can arise from a heightened response to the aversive stimulus, indicative of *hypersensitivity*. However, an average increase in the response to an aversive stimulus can also be the result of reduced habituation over repeated exposures: Lonely and non-lonely people might initially respond equally extreme to an aversive stimulus, but if the non-lonely people habituate quickly, while the lonely people keep showing unhabituated ongoing *hyperalertness* to the aversive stimulus, the average response over the entire set of exposures will be higher for the lonely than the non-lonely people. Distinguishing between hypersensitivity (more extreme responding to individual/ initial exposure to an aversive stimulus) and hyperalertness (less habituation to aversive stimuli over time) is therefore crucial to understand the cognitive processes that underly the causes and consequences of loneliness.

To be able to study both hyperalertness and hypersensitivity in one paradigm, the proposed study will employ a roving oddball paradigm to distinguish between responses to novel and repeated negative social stimuli. In contrast to the classic oddball, in a roving oddball paradigm each stimulus is repeated several times to serve as both the deviant and the standard. Thereby, it is possible to assess the response to the initial presentation of the stimulus (deviant), charting potential effects of hypersensitivity to negative social stimuli in lonely people. Moreover, this paradigm measures the adaptation to the same stimulus over repeated exposures, charting potential effects of hyperalertness to negative social stimuli in lonely people.

We expect to find evidence for both hypersensitivity and hyperalertness in lonely people. Hypersensitivity will show up as greater neural responses to the *first exposure* to a negative social stimulus as compared to a positive social stimulus (hypothesis 1), based on previous work that suggested an attentional bias for negative social stimuli (Bangee et al. 2014; S. Cacioppo, Balogh, and Cacioppo 2015; J. T. Cacioppo et al. 2009; Grennan et al. 2021). Further, we expect to find hyperalertness in lonely people, i.e, slower adaptation to *repeated exposure* to negative social stimuli (hypothesis 2). We thus predict that both cognitive effects of loneliness exist side by side, such that lonely people show a heightened response to the first presentation of a negative social stimulus *and* slower adaptation to repeated exposures.

A deeper comprehension of these neurocognitive mechanisms in loneliness is crucial for developing effective intervention strategies (S. Cacioppo et al. 2015). The differentiation between hypersensitivity and hyperalertness has distinct implications for treatment approaches. While exposure through increased social contact might be effective in diminishing hypersensitivity by reducing the intensity of initial reactions to negative stimuli, it may not be as beneficial for hyperalertness, where repeated exposure fails to lessen the response. On the contrary, techniques focusing on relaxation and mindfulness (Lindsay et al. 2019) could be more appropriate for managing hyperalertness, aiding in the regulation of chronically elevated stress responses. This nuanced understanding is essential in tailoring interventions to effectively address the complex nature of loneliness and its varied psychological impacts.

2. Materials & Methods

This report comprises two distinct studies. Study 1 focuses on identifying specific channels and time intervals that are responsive to emotional facial expressions and their repetition. Participants in Study 1 are selected from the general population. On the other hand, Study 2 aims to explore variations in social processing related to loneliness. In Study 2, participants undergo screening to determine their loneliness scores. The EEG analysis in Study 2 utilises the time intervals and channels of interest that were initially pinpointed in Study 1.

2.1 Participants

2.1.1 Study 1: Establishing neural effects

The initial sample consisted of 38 participants. Two participants were excluded because of technical problems that affected the quality of their EEG recording. The final sample consisted of 36 participants (22 female, Age [years]: mean=23.67, std=5.93, range: 19-54). The study was conducted in accordance with the Declaration of Helsinski and the British Psychological Association's Code of Ethics and Conduct. All participants provided written informed consent. Participants received compensation at a rate of £12.50 per hour. This study was approved by the Research Ethics Committee at Royal Holloway, University of London (Project ID: 3126).

2.1.2 Study 2: Comparing lonely and non-lonely people

For study 2, we plan to compare lonely and non-lonely participants. We will employ an enrichment sampling approach to maximise the difference between participants in loneliness. To this end, we will recruit a group of lonely participants who score above the 90^{th} percentile on the UCLA Loneliness Scale-3 (ULS-3) and a group of non-lonely participants who score below the median. To determine the ULS-3 cut-off scores, we utilise data from representative sample of 962 participants that were collected for a related behavioural study (Pascalidis & Bathelt, 2024). Based on these data, we plan to set the cut-off value for the non-lonely group at 50 (exact percentile score: 48) and the cut-off for the lonely group at 65 (exact percentile score: 63).

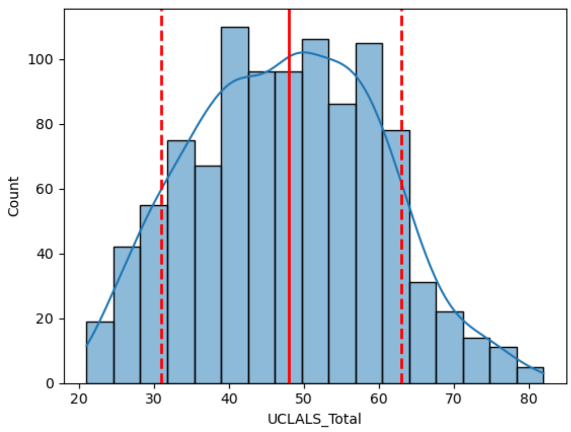

Figure 1 Distribution of UCLA Loneliness Scale Total scores in a representative sample of 962 people. The solid red line indicates the median score. The dashed lines indicate the 10^{th} and 90^{th} percentile. The bars show the histogram of the scores. The curve shows the fit of a kernel density estimation with a Gaussian distribution.

We will recruit participants through local advertising, including in public libraries and community centres, using leaflets and posters. We aim for 50 participants per group, with an additional contingency of 10 participants per group to account for potential data loss (120 total). The sample size in published EEG studies of hypersensitivity to negative social stimuli in loneliness spanned a wide range, i.e. 30 (Du et al. 2022), 70 (S. Cacioppo, Balogh, and Cacioppo 2015), 147 (Grennan et al. 2021). The effect sizes from these studies cannot directly inform the current study because of differences in the experimental paradigm and analysis approach, e.g. microstate analysis (S. Cacioppo, Balogh, and Cacioppo 2015) or correlational design (Grennan et al. 2021). Further, in contrast to Grennan et al. (2021), we will employ an enrichment sampling approach that will maximise the behavioural differences between the groups i.e., we will screen people for loneliness, and only invite those on the relative extremes of the loneliness spectrum to participate in the EEG study. Therefore, a smaller sample size will suffice to detect between-group differences.

The power of event-related potential (ERP) studies depends not only on the sample size but also on the number of trials that are used to derive the ERP (Baker et al. 2021). A previous study investigated the influence of sample size and trial number on the power to detect difference in the N170 (Jensen and MacDonald 2023). Their results suggest that a between-participant difference with a medium effect size (2μV difference) can be detected with >80% power with a total of 32 participants using 56 trials (Jensen and MacDonald 2023). The authors also report that high statistical power can be achieved for the N400 with 42 trials and 20 participants at a moderate effect size (2.25μV difference). Further, Gibney and colleagues found that a small effect size difference in the LPP (0.6μV) can be detected with >80% power with a sample of 100 participants per group and 15 trials. Based on these results, we plan at least 50 trials per condition (increased to 50 to account for lost trials due to blinks, movement, etc.) to ensure that we have enough trials to adequately characterise the N170 and LPP components. This number of trials was sufficient to identify significant expression and repetition effects in Study 1.

2.1.3 Inclusion and Exclusion Criteria

Participant characteristics:

- having received or receiving treatment for disorders like anxiety or depression in the last 6 months[1].
- diagnosis of a health condition that require ongoing medical treatment, such as autoimmune disorders, uncontrolled diabetes, liver and kidney disease, cancer, and conditions requiring chronic immunosuppressive therapy, or that confer a disability status, such as severe asthma, chronic pain, or musculoskeletal disorders[2]
- history of psychiatric disorders, except anxiety and depression.
- history of neuropsychological injury.
- history of neurosurgical procedure or eye surgery.
- taking prescribed or non-prescribed medications, besides oral contraceptives.
- ongoing anti-malarial treatment.
- visual impairment that cannot be corrected to the typical range.
- significant hearing loss that cannot be corrected to the typical range.
- having a hairstyle that prevents the placement of EEG sensors on the scalp, such as braids, dreadlocks, or ornamentation that cannot be removed.

[1] Loneliness is highly comorbid with anxiety and depression. Therefore, excluding participants with any history of anxiety or depression would heavily bias the sample. However, we exclude participants who are receiving treatment or recently received treatment as this may impact their response.
[2] Chronic health conditions are excluded because the reasons and mechanism of loneliness may be different to loneliness in the general population.

Acute exclusions[3]:

- consumed more than 3 units of alcohol in the 24 hours before the session.
- consumed alcohol before the session.

- consumed more than one cup of coffee or other sources of caffeine in the hour before the session.
- recreational drugs use in the 24 hours before the session.
- very little sleep (less than 6 hours) in the night before the session.

[3] These criteria may affect the quality of the data that can be collected from participants. Participants will be informed about these criteria several days before their scheduled appointment. When possible, we will re-schedule the appointment if these criteria are not met on a particular day.

Data quality:

- did not complete the EEG task.
- less than 90% accuracy on the target detection task.
- EEG data set deemed unusable based on inspection of the raw EEG data by two independent researchers who are unaware of the group assignment and are not authors. The researchers will assess if high-frequency noise, low-frequency drift, or flat-lining is present in more than 10 channels.[4]
- more than 4 EEG channels marked as bad by the RANSAC algorithm.
- fewer than 50 epochs in any condition after artefact detection through the AUTOREJ algorithm.

[4] We mostly employ automated and well-documented procedures to enhance the replicability of the results. However, the algorithms employ statistical threshold to determine the difference between good-quality and poor-quality data. This can fail when little good data are available. Therefore, we employ blinded inspection of the raw data by two independent researchers. The inspection assessed if there was high-frequency noise or no signal in more than 10 channels and if there was significant movement- or muscle-related artefact in more than half of the recording. Cases of disagreement between the two researchers will be included, unless they fail to meet the other criteria. All datasets will be included in the data release alongside the quality metrics regardless of their inclusion in the analysis.

2.2 Behavioural Measures

Loneliness: We assess loneliness using the UCLA Loneliness Scale version 3 (Russell 1996). The UCLA Loneliness Scale 3 (ULS-3) is a commonly used measure to assess loneliness. It is a self-report questionnaire with 20 items. Respondents rate each item on a 4-point Likert scale. The ULS-3 has shown high Cronbach's alpha coefficients, typically ranging from 0.80 to 0.94 (Russell 1996).

Social Isolation: To distinguish loneliness from social isolation, we assessed social network size using the abbreviated version of the Lubben Social Network Scale with 6 items (J. E. Lubben and Gironda 2000). The LSNS-6 has shown good internal consistency with Cronbach's alpha coefficients between 0.80 and 0.89 for different subscales (J. Lubben et al. 2006).

Perceived Stress: Perceived stress can influence people's emotional response and reactivity. To distinguish the effect of loneliness from perceived stress, we will administer the Perceived Stress Scale (PSS). The PSS is a widely used self-report scale designed to measure the degree to which situations in one's life are appraised as stressful. The scale has strong psychometric properties, with a Cronbach's alpha coefficient ranging from 0.74 to 0.86 (Cohen, Kamarck, and Mermelstein 1983).

Mental Health: We administered additional mental health measures to characterize the sample. For study 1, we assessed social anxiety and depression using the Social Anxiety Interaction Scale (Mattick and Clarke, 1998), and the depression subscale of the Depression Anxiety Stress Scale (Lovibond and Lovibond, 1996) respectively. The SIAS includes 20 items rated on a 5-point Likert scale and shows high reliability. One item was rewarded to be more inclusive (Lindner and Martell, 2013). The DASS-D

has 14 items rated on a 4-point Likert scale, displaying excellent reliability (Cronbach's alpha: 0.94, Antony et al., 1998).
For study 2, we will employ different questionnaires to assess anxiety and depression. The reason for this change is that we want to use questionnaires that are recommended as a common measures across studies of mental health in adults (see wellcome.org). Namely, we will use the Patient Health Questionnaire – Depression (PHQ-9, Kroenke et al. 2010) to assess depression, and the General Anxiety Disorder questionnaire (GAD-7) to assess anxiety (Spitzer et al. 2006). The GAD-7 is a widely used self-report questionnaire designed to assess the severity of generalized anxiety disorder symptoms. Respondents rate each item on a 4-point Likert scale based on how often they experience certain symptoms over the past two weeks. The scale typically demonstrates a high Cronbach's alpha coefficient, often ranging from 0.85 to 0.92, indicating strong internal consistency and reliability (Spitzer et al. 2006). The PHQ-9 is a widely used self-report questionnaire designed to assess the severity of depressive symptoms. Respondents rate each item based on how frequently they have experienced certain symptoms over the past two weeks. The scale typically demonstrates a high Cronbach's alpha coefficient, often ranging from 0.82 to 0.89, indicating strong internal consistency and reliability (Kroenke et al. 2010). We will also administer the SIAS to obtain a specific measure of social anxiety (L. Peters 2000). In addition, we will administer the Brief Symptom Inventory (BSI) as an indicator of general psychological distress (Derogatis and Melisaratos 1983). The Brief Symptom Inventory (BSI) is a comprehensive self-report questionnaire developed to evaluate a broad range of psychological symptoms. The scale shows strong psychometric properties with a high Cronbach's alpha coefficient, ranging from 0.71 to 0.85 (Derogatis & Melisaratos 1983).

Demographic information: We will administer a custom questionnaire to obtain demographic information that characterises our sample. Specifically, we will ask participants for their age, gender, handedness, ethnicity, and socioeconomic status (SES). We will collect the minimum necessary information for each question in line with recommended ethical and data security standards. For instance, we will only ask participants for their month and year of birth to determine their age. For gender and ethnicity, we will use recommended inclusive items (MRC Cognition & Brain Sciences website). To assess handedness, we will use 4 items from the Edinburgh Handedness Inventory (Veale 2014). For SES, we will ask about the number of years of education as this is the most reliable measure of SES for samples that include many people who are not in full time employment (Diemer et al. 2013).

Image ratings: To assess potential differences in how facial expressions are perceived by lonely or non-lonely people, we will ask participants to rate each stimulus along dimensions of valence, arousal, and dominance. We will use Self-Assessment Manikin scales for these ratings (Morris 1995). The ratings will be completed after the roving oddball task.

2.3 Stimulus Material & Experimental Procedure

Face stimuli were taken from the FACES database (Ebner, Riediger, and Lindenberger 2010). The FACES database consists of naturalistic faces of young, middle-aged, and older women and men (N=171). Each face is represented with two sets of six facial expressions (neutral, sad, disgusted, afraid, angry, and happy). Ratings of discriminability of the facial expressions by young, middle-aged, and older women and men (N=154) are included in the database.
For the current experimental design (study 1 and 2), we selected angry and happy facial expressions across age groups that were recognized with at least 90% accuracy by male and female raters. We used the MatchIt package v4.5.4 for R to match select subsets of stimuli for each facial expression that were matched for accuracy ratings across male and female raters. The final set consisted of 72 unique stimuli. The full list of identification numbers is included in the associated OSF repository.
We standardized the stimuli to remove low-level visual confounds. First, we aligned the images and created oval masks to remove extraneous features using the webmorphR v.0.1.1 package for R. To that end, we identified facial landmarks using automatic delineation, aligned image to the centre using

Procrustes rotation, and converted images to greyscale. Second, we applied luminance matching to the foreground of the images using the SHINE toolbox for Matlab (Willenbockel et al. 2010). The code for the stimulus selection and preprocessing pipeline is available via the associated OSF repository. Subsequently, applied an oval mask that removed the hair and neck. We used the average value across all images to determine the background colour. This was intended to minimise harsh contrasts between stimuli that may cause participants to blink.

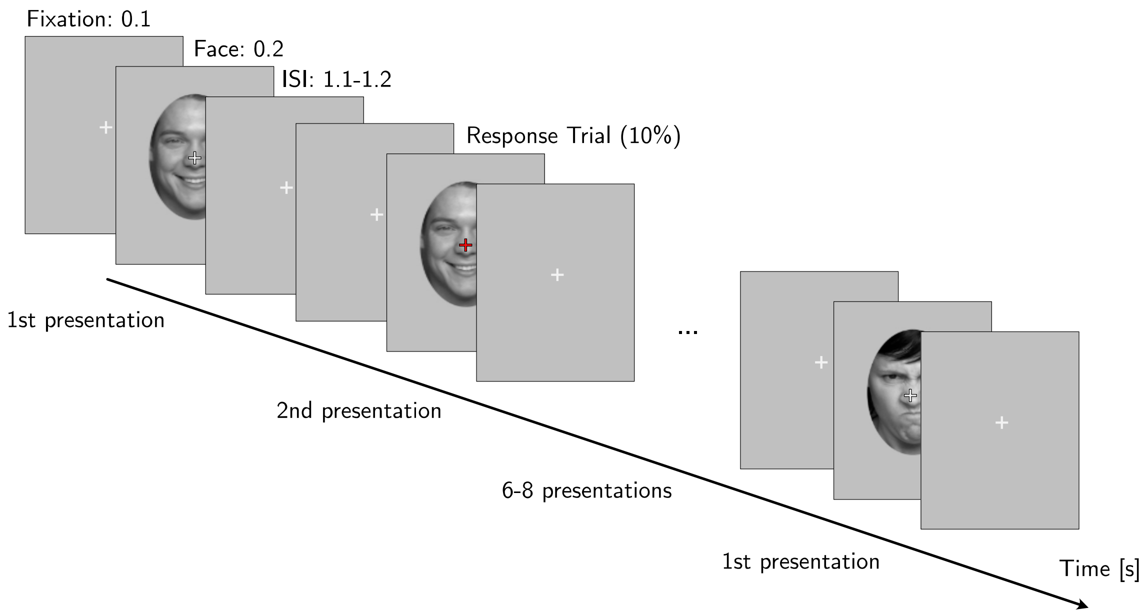

Figure 2 Illustration of the roving oddball paradigm. Pictures of emotional facial expressions were repeated between 6 and 8 times. In 10% of trials, the fixation cross superimposed on the face was shown in red. Participants were instructed to press a button in these trials. Abbreviations: ISI – intertrial interval.

In the roving oddball paradigm, each facial expression image was presented between 6 and 10 times. The exact number of repetitions and the sequence of expressions was randomly determined. For each repetition train, the stimulus is presented at least 5 times. As the number of repetitions increases beyond five, the probability of continuing with the same stimulus decreases by 25% with each additional presentation. This probabilistic rule helps in varying the stimuli exposure and maintaining a degree of unpredictability in the sequence of stimuli presented during the experiment. The entire task sequence included 1500 trials. Trains of angry faces were presented 76 times and trains of happy faces were presented 65 times. The same trial sequence was used for all participants. For the analysis, we consider emotion and repetition as experimental conditions, i.e. responses are averaged to collapse other dimensions of the stimuli such as identity, age, and gender. Each trial began with a fixation cross presented for 0.1s presented with a size of 0.4-by-0.4 degrees of visual angle (DVA). Subsequently, a facial expression was presented for 0.2s with a size of 5.7 by 8.1 DVA. Finally, a fixation cross was presented again with a randomly jittered duration between 1.1 and 1.2s. The trial sequence was split into 4 blocks of 375 trials to allow participants to rest.

A fixation cross was superimposed on the facial expression images. In 10% of trials, the fixation cross appeared red instead of white. Participants were instructed to press the space bar as quickly as possible when they notice this change. This task was included to check participants engagement throughout the task. Participants completed a practice at the beginning that only contains white and red fixation crosses with equal probability of red and white crosses. Participants completed a minimum of 10 practice trials and were only allowed to proceed if they respond correctly in 80% of practice trials. Participants received feedback on their performance on the target detection tasks after sets of 10 trials during the practice and at the end of each block in the main tasks. Trials during which button presses occurred or were supposed to occur were excluded from the ERP analysis due to the movement confound.

The experiment were implemented in PsychoPy (Peirce 2007). The script is available via the associated OSF repository.

2.4 EEG

2.4.1 EEG recording

Participants were seated comfortably in a dimly lit and sound-attenuated room. EEG activity was recorded using a Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands) with 64 channels. The electrode cap, which contained 64 active electrodes, was placed on each participant's head following the standard 10-20 system for electrode placement. To ensure stability during the recording session, the cap was secured using an adjustable strap.
To capture eye movements and blinks, four facial electrodes were used to record the electrooculogram (EOG). Horizontal eye movements were measured using two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements and blinks were measured using two electrodes placed approximately 1 cm above and below the right eye. Additionally, an electrode was placed below the left clavicle to record the electrocardiogram (ECG) for the removal of cardiac artefacts.
To improve the signal-to-noise ratio, the EEG signal was preamplified at the electrode with a gain of 1 using the BioSemi ActiveTwo system. This preamplification also corrected for high impedances at each electrode, eliminating the need for impedance measurements. However, to adhere to Biosemi's recommendations, the offset voltage between the A/D box and the body was maintained between 25 and 50 mV. The EEG amplitude was kept within 50 µV. Each active electrode was measured online with respect to a common mode sense active electrode, resulting in a monopolar (non-differential) channel configuration. The data was digitized at 24-bit resolution with a sampling rate of 512 Hz. No hardware filters was used for the recording.

2.4.2 EEG processing

To ensure reproducibility of our results, we employed an automated processing pipeline that follows recommended practices for EEG data analysis (Jas et al. 2018). The processing were carried out using MNE Python (Gramfort et al. 2014). The pipeline contained the following steps:

1. Bandpass filter: 0.5-40Hz using a linear-phase Finite Impulse Response (FIR) filter with delay compensation.
2. Independent Component Analysis (ICA) with 25 dimensions. Components that correlate highly with EOG or ECG signals will be removed using adaptive z-scoring (*find_bad_eog*, *find_bad_ecg* in MNE Python).
3. Epoching: -0.1 to 1.0s window, an offset will be added based on a timing accuracy test.
4. Bad channel detection using the Random Sample Consensus (RANSAC) algorithm (Bigdely-Shamlo et al. 2015).
5. Bad epoch rejection using the Autoreject algorithm (Jas et al. 2017) with 6 interpolation steps.
6. Referencing to the average reference.

We evaluated the number of trials available for analysis after EEG processing. For the angry emotion category, the mean number of trials for the first repetition was 67.08 (SD = 7.03), with a minimum of 34 and a maximum of 73 trials. In the fifth repetition for the same emotion category, the mean number of trials was 68.77 (SD = 7.17), with a range from 37 to 75 trials. Regarding the 'happy' emotion, the first repetition showed a mean of 53.03 trials (SD = 5.30), with the number of trials ranging from 35 to 58.

The fifth repetition for 'happy' had a slightly lower mean of 52.90 trials (SD = 6.31), and trials varied between 28 and 58.

We averaged the trials for each participant, producing event-related potential responses for both emotion categories: angry and happy. These were averaged over the 1st and 5th repetitions. Similarly, responses for the 1st and 5th repetitions were averaged across emotion types. The number of trials were equated during the averaging stage. The condition with the least responses determined the number of trials for all conditions, and the other condition(s) were subsampled through random selection of trials. From these averages, we generated difference waves that highlight increased responses to angry faces (by subtracting happy from angry) or the initial presentation (subtracting the 5th from the 1st repetition). An HTML report detailing all preprocessing steps was made for every participant and shared on the OSF repository.

2.5 Statistical Analysis

2.5.1 Study 1

Our aim was to spot group-level clusters that significantly vary between conditions like emotion type and repetition count. These results are intended to inform the channels and time windows of interest for Study 2. We used the 'permutation_cluster_1samp_test' function from MNE Python for this. It runs a one-sample t-test to determine if the difference wave significantly deviates from 0. By comparing this to a null hypothesis based on 5,000 permutations, it identified significant clusters in both space and time, in line with recommended guidelines (Jas et al. 2018). We extracted the channels and time windows in each cluster to compare lonely and non-lonely participants in an independent sample in Study 2.

2.5.2 Study 2 – Main Analyses

We will extract the mean ERP amplitudes for any spatiotemporal cluster that showed a significant effect of emotion or repetition in Study 1. Namely, we will focus our analysis for hypersensitivity on averaged ERP responses to the time window 120-170ms (electrode list: CP5, CP3, CP1, P1, P3, P5, P7, PO7, O1, Oz, POz, Pz, CPz, CP4, CP2, P2, P4, P6, PO8, PO4, O2), time window 360-470ms (electrode list: C4, TP8, CP6, CP4, P4, P6, P8, PO8), time window 480-600ms. The analysis for hyperalertness will focus on the average difference between the first and fifth exposure in time window 480-600 (electrode list: POz, F8, FC6, C4, C6, T8, TP8, CP6, CP4, CP2, P2, P4, P8, P10, PO8, PO4, O2). For each spatiotemporal cluster, we will fit a mixed-effects analysis of variance (ANOVA) model with within-subject factors for emotion (angry, happy) and repetition (1^{st}, 5^{th}) and a between-subject factor of group (lonely, non-lonely). We will use post-hoc t-tests to compare the mean ERP amplitudes between the participant groups. We will employ Bonferroni correction to account for multiple comparisons in the different spatiotemporal clusters. A significance criterion of $\alpha < 0.02$ will be used.

For hypothesis 1, we expect that lonely people show increased sensitivity to angry over happy facial expression. This is operationalised as an increased ERP mean amplitude to deviant angry faces in spatiotemporal clusters that showed significant differences between angry compared to happy faces in Study 1.
For hypothesis 2, we expect that lonely people show reduced habituation when being repeatedly exposed to angry facial expressions, while the habituation is expected to be stronger for happy expressions. This is operationalised as a significant expression-by-repetition interaction in spatiotemporal clusters that either show an effect of emotion or repetition in the Study 1.

Table 1 Registered Report Design Template.

Question	**Hypothesis**	**Sampling Plan**	**Analysis**	**Rationale for deciding the sensitivity of the test for confirming or disconfirming the hypothesis**	**Interpretation given different outcomes**	**Theory that could be shown wrong by the outcomes**
Do lonely people show hypersensitivity to social threat?	H1: Mean amplitude to angry faces is significantly higher at the *first* repetition and greater in lonely people compared to non-lonely people, and this difference is greater compared to mean amplitude in the response to happy faces.	We will collect the whole sample before conducting the analysis. The rationale for the sample size is described in Section 2.1.2	To confirm H1, a significant interaction between emotion condition, repetition, and participant group needs to be identified in the mixed-effects analysis (see above). A post-hoc t-test will be used to confirm the direction of the effect by comparing the mean ERP amplitude for the *first* presentation of angry faces between the lonely and non-lonely groups. This t-test needs to be significant, and the mean amplitude needs to be higher in the lonely group.	We expect a medium effect size based on previous research (S. Cacioppo, Balogh, and Cacioppo 2015; Du et al. 2022).	If we do not find support for H1, we will conclude that lonely people do not show increased responses to potentially threatening social stimuli (hypersensitivity).	According to the evolutionary framework, loneliness is thought to make people more alert to potentially threatening social cues. If we find no increased amplitude for angry faces in the lonely group at the first repetition, our result would go against the hypersensitivity interpretation of the evolutionary framework.
Do lonely people show slower adaptation to social threat?	H2: Mean amplitude to angry faces at the *fifth* repetition is significantly higher in lonely people compared to non-lonely people, and this difference is greater compared to mean amplitude in the response to happy faces.		To confirm H2, a significant interaction between emotion condition, repetition, and participant group needs to be identified in the mixed-effects analysis (see above). A post-hoc t-test will be used to confirm the direction of the effect by comparing the mean ERP amplitude for the *fifth* presentation of angry faces between the lonely and non-lonely groups. This t-test needs to be significant, and the mean amplitude needs to be higher in the lonely group.		If we do not find support for H2, we will conclude that lonely people do not adapt more slowly to potentially threatening social stimuli (hyperalertness).	A non-significant result would argue against the hyperalertness interpretation of the evolutionary framework.

2.5.3 Study 2 – Exploratory Analyses

Loneliness is distinguishable from but closely related to social anxiety and depression (Fung, Paterson, and Alden 2017). To establish the specificity of the observed effects for loneliness, we will conduct additional exploratory analyses that control for social anxiety and depression. Further, loneliness is defined as a subjective state that is not necessarily connected to objective social isolation (Perlman and Peplau 1981). To establish the specificity of the subjective evaluation, we will repeat the main analysis controlling for social isolation as assessed by the Lubben Social Network Scale (Lubben and Gironda 2000) and perceived stress as assessed by the Perceived Stress Scale (Cohen, Kamarck, and Mermelstein 1983).

For these control analyses, we employed an analysis of covariance (ANCOVA) model with ERP amplitude as the dependent variable, lonely versus non-lonely as the independent variable, and continuous social anxiety, depression, social isolation, and perceived stress scores as covariates. Significant effects of the covariates on ERP amplitudes were followed up with mediation analyses within each group (lonely and non-lonely). These analyses assessed the direct and indirect effects of continuous loneliness scores on ERP amplitudes, including each covariate separately as potential mediators.

The repetition effect in Study 1 was lateralised to the right hemisphere (see Figure 1c). To assess the impact of differences in brain lateralisation, we collected handedness information to assess the impact of handedness differences on the results of Study 2.

2.6 Open Science

All materials are shared via an OSF repository. The exception are the processed face stimuli, because accessing the FACES database requires permission from the original authors. In lieu of sharing the processed images, we will share the identification numbers of the images included in this study and the code for processing images. Link to OSF repository:
https://osf.io/c2svz/?view_only=4ee744ac88c74f41a4d955824a69284b

The EEG data is stored in EEG-BIDS format (Pernet et al. 2019) and stimulus presentation codes follow the hierarchical event descriptor guidelines (Robbins et al. 2021). The EEG data is available via OpenNeuro.org. Link to OpenNeuro repository:
Study 1: doi:10.18112/openneuro.ds004802.v1.0.0

3. Results

3.1 Study 1

3.1.1 Sample characteristics

All participants scored within the typical range for loneliness (UCLA Loneliness Scale: >65 indicates high loneliness, mean=47.36, SE=1.800). For depression, all participants fell within the normal range (DASS-D: <10 normal range, mean=0.56, SE=0.091). For social anxiety, 8 participants scored above the clinical cut-off (SIAS: >36 cut-off, mean=23.39, SE=2.694).

3.1.2 Response to emotion category and repetition in the roving oddball task

The mean amplitude in response to happy and angry faces decreased with the number of repetitions. To characterise the effect of repetition, we focused on the contrast between the first repetition and the the 5^{th} repetition. We chose the 5^{th} over the 6^{th} repletion, since the 6^{th} repetition only occurred in a relatively small subset of trials, due to random allocation of number of repetitions (varying between 6 and 10 repetitions) for each trial. We identified two spatiotemporal clusters that showed a significantly increased ERP amplitude for angry faces. This included an early time window between 120 and 170ms with differences in posterior and central channels (CP5, CP3, CP1, P1, P3, P5, P7, PO7, O1, Oz, POz, Pz, CPz, CP4, CP2, P2, P4, P6, PO8, PO4, O2) and a later time window between 360 and 470ms with differences in right posterior channels (C4, TP8, CP6, CP4, P4, P6, P8, PO8, see Figure 1 a-b). These results are in line with the published literature that indicated enhanced N170 and LPP responses in response to angry facial expressions (Kujawa et al. 2015; Schupp et al. 2004; O'Toole et al. 2013; Krombholz, Schaefer, and Boucsein 2007).

We also identified one cluster that showed a significantly greater ERP amplitude for the first presentation of a stimulus compared to the 5^{th} presentation, collapsed over angry and happy facial expressions (see Figure 1 c). This difference was observed over right posterior and central channels between 480 and 600ms (POz, F8, FC6, C4, C6, T8, TP8, CP6, CP4, CP2, P2, P4, P8, P10, PO8, PO4, O2). This finding is consistent with the literature of repetition effects in paradigms with face stimuli that typically report reduced amplitudes with repeated exposure between 300 and 600ms over central and parietal channels, indicative of the N400 component (see Schweinberger and Neumann 2016 for a review).

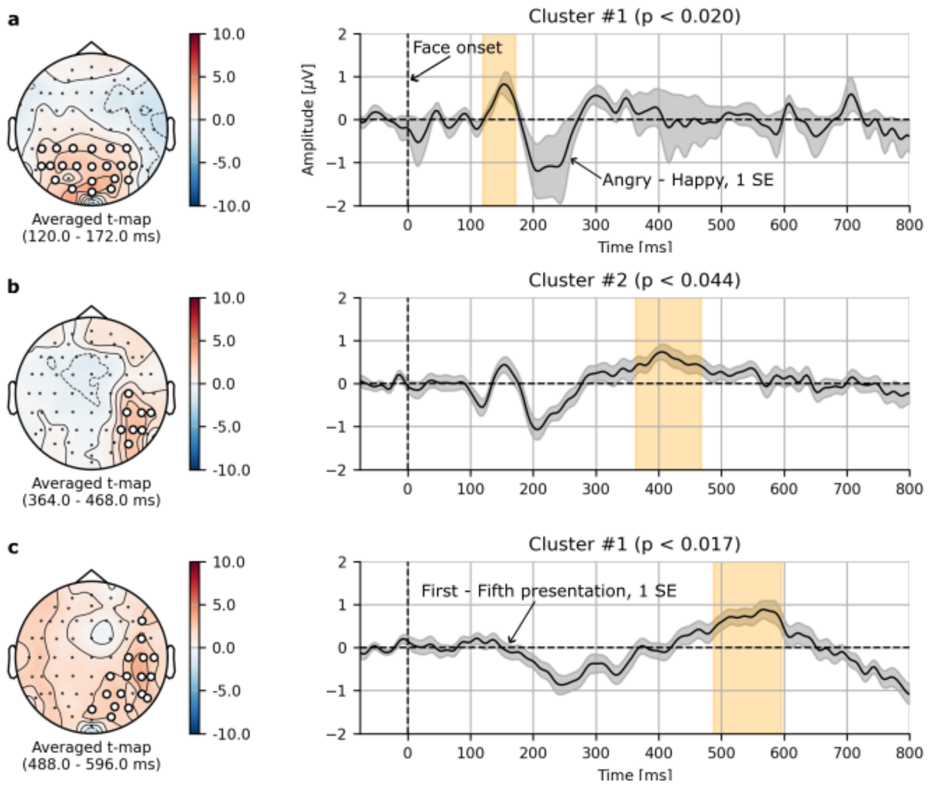

Figure 3 Spatiotemporal clusters that showed significant differences by emotion (a,b) and by repetition (c) in the pilot study. The left panel shows the topography of the statistical effect. The right panels shows the difference wave for angry – happy, collapsed across repetitions (a,b), and for 1st – 5th presentation (c). The grey shaded area shows the standard error. The yellow shaded area indicates the time window for the spatiotemporal cluster. The statistical comparison was based on a one-sample t-test (for further details please see Study Protocol).

3.2 Study 2

3.2.1 Sample characteristics & Performance

Description of the sample characteristics. Performance on the detection task and difference in image ratings between the lonely and non-lonely groups.

Table 2 Descriptive statistics and comparison between the lonely and non-lonely groups.

	lonely (n=)	non-lonely (n=)	comparison
Age [years] (mean [sd])			
Gender			
Man (n, %)			
Woman (n, %)			
Other (n, %)			
Handedness (mean [se])			
Ethnicity			
Asian (n, %)			
African (n, %)			
Indigenous (n, %)			
Latin (n, %)			
Middle Eastern (n, %)			
Pacific Islander (n, %)			
White (n, %)			
Other (n, %)			
Undisclosed (n, %)			
Years in education (mean [se])			
Loneliness (UCLA-LS)			

Total mean (mean [se])	
Intimate mean (mean [se])	
Social mean (mean [se])	
Existential (mean [se])	
Social Isolation (LSNS) (mean [se])	
Depression (PHQ-9) (mean [se])	
Social Anxiety (GAD-7) (mean [se])	

3.2.2 Sensitivity to angry facial expression in lonely people (hypothesis 1)

3.2.3 Habituation to repeated exposure in lonely people (hypothesis 2)

3.2.4 Exploratory analyses to assess the effect of social isolation, mental health symptoms, and perceived stress

4. Discussion

Discussion points for the main manuscript include:

- Interpretation of the findings with respect to the published literature on neurophysiological correlates of loneliness, specifically the importance of distinguishing between hypersensitivity and reduced habituation. The relevant studies are described in the introduction. Relevant studies that are published after the acceptance of the Stage 1 report will be integrated in the discussion.
- Interpretation of control analyses to establish the specificity of the association between loneliness and social processing, highlighting potential unique and shared mechanisms in loneliness with reference to the relevant literature in social anxiety, depression, and perceived stress.
- Interpretation of control analyses considering individual differences in hypervigilance and hypersensitivity
- Limitations of the study: representativeness of the sample, confounds of other mental health conditions, ecological validity of the experimental paradigm
- Implication of the findings for interventions that aim to reduce chronic loneliness.

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