Master's Thesis of Psychology

Neural Pattern Signature of Social Exclusion Predicts Loneliness in Older Adults

사회적 배제의 신경반응패턴과
노년기 고독감의 관계

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오나은

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Abstract

Social isolation is a critical factor that impacts our mental and physical health in late-life. A specific instance of social isolation is the experience of being ignored or unnoticed by others, namely social exclusion. As the brain is the key organ for forming and maintaining salutary connections with others, understanding the brain mechanisms of social exclusion is important for understanding psychological processes that would complement the existing self-report measures. In addition, examining the relationship between the neural signature response of social exclusion and loneliness outcome can provide insight into the social cognitive aspect of loneliness. This study aims to identify a neural pattern signature of social exclusion in older adults, using multivariate pattern analysis of neural activations during a Cyberball task, and to verify loneliness-related individual differences in the signature. A predictive model was developed to distinguish between a social exclusion and inclusion condition, using a widely distributed neural activation pattern of 88 older adults. The fMRI pattern classifier distinguished social exclusion and inclusion with an accuracy of 0.632 and AUC of 0.693. Voxel-level and region-level feature importance analysis demonstrated that areas contributing most to the prediction are the bilateral inferior parietal lobe, dorsomedial prefrontal cortex, precuneus, amygdala, and the ventral striatum. In relation to individual differences in loneliness, those who perceived more loneliness showed higher neural signature responses during social exclusion. These findings demonstrate that the neural signature of social exclusion is characterized by distributed networks of functional regions, especially the mentalizing and amygdala networks, and that older adults who are lonely may be more sensitive to being socially excluded.

Keywords : social exclusion, loneliness, multivariate pattern analysis (MVPA), older adults
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Chapter 1. Introduction

1.1 Social Isolation

Humans are social beings that are greatly affected by social relationships, processes, and behavior. We are intrinsically driven by a desire to form and maintain social connections (Baumeister & Leary, 1995; James, 1890) and social factors can be caring and protective. Thus, social isolation, i.e. being physically or emotionally separated from others, can be a critical threat to mental and physical health. It is known to be related to depression (Cacioppo et al., 2006; VanderWeele et al., 2011), alcohol abuse (Åkerlind & Hörnquist, 1992), suicidal ideation (Rudatsikira et al., 2007), social anxiety (Kearns et al., 2014), and impulsivity (Savci et al., 2015). It is also a risk factor of cognitive decline and dementia (Kim, 2015; Wilson et al., 2007), cardiovascular health (Cacioppo et al, 2002; Valtorta et al., 2016), reduced immune function (Kiecolt-Glaser et al., 1984, Cacioppo et al., 2015), and the increased likelihood of mortality (Holt-Lunstad & Smith, 2018).

The impact of social isolation is especially consequential in late-life. Loneliness, a perceived feeling of isolation, is generally retained at a constant level until the age of 65 but rapidly increases in the old-old population (Mund et al., 2019). It is prevalent in older populations accounting to 30% of elders reporting the feeling of loneliness (Yang & Victor, 2008).

1.2 Social Exclusion

Social exclusion is a pointed, specific instance of social isolation. It is the experience of being ignored or unnoticed by others. We experience being socially

excluded from others in everyday life, such as being uninvited to a social outing, one's requests being ignored, or being bullied in a social group. Many of these threats to social connections are subtle, ambiguous, and sometimes unintentional (Banki, 2012; Kerr & Levine, 2008; Richman & Leary, 2009). This is a distinct type of social isolation that is different from other types of social isolation experiences, such as being explicitly rejected via cues that one is not wanted in a social relationship (Williams, 2007). Social exclusion results in negative psychological outcomes such as feeling ignored, excluded, hurt, sad, or angry, and can lead to depression and alienation in the long run. The experience of social exclusion, or ostracism, can be measured through experimentally administered social situations, in which participants are led to believe they are being ignored or unnoticed by others. One well-known task that induces ostracism is the Cyberball paradigm where participants experience exclusion when they stop receiving the ball from other players during a virtual ball-tossing game (Hartgerlink et al., 2015).

1.3 Neural Mechanism of Social Exclusion and Loneliness Outcome

In the social neuroscience perspective, the brain is the key organ for forming, monitoring, maintaining, repairing, and replacing salutary connections with others (Cacioppo & Berntson, 1992). Understanding the how the brain processes and reacts to information during social exclusion can provide an additional window into psychological processes that complement self-report measures or biological measures (Berkman & Falk, 2013). It is especially useful in situations where the underlying psychological processes are difficult to capture when utilizing other methods, such as populations that find it challenging to express vague emotions with words. Using the brain as a predictor of the psychological state (e.g. social exclusion)

is a modeling approach that is consistent with this perspective. This 'decoding' model extracts latent, psychological factors as functions of brain data via transformation of high-dimensional brain data into a potentially low-dimensional representation in which they exhibit certain desired characteristics, e.g. good classification (Haufe et al., 2014).

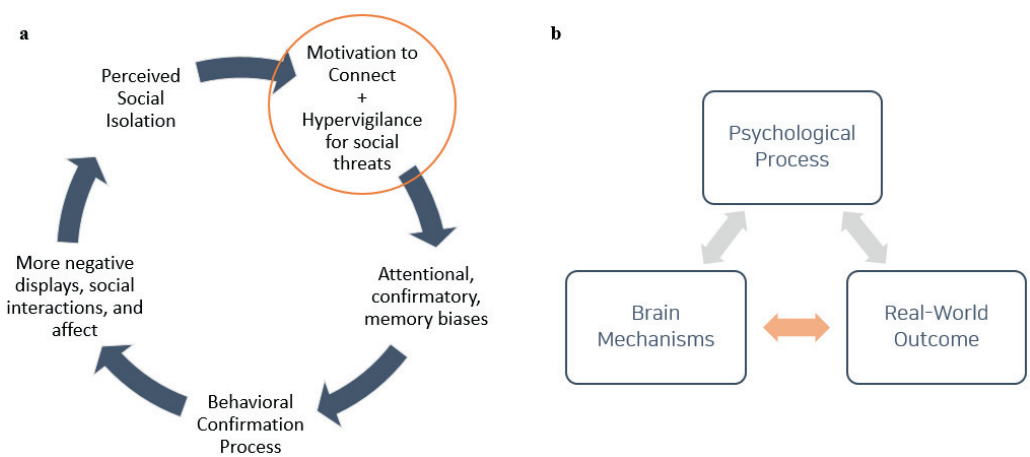
Moreover, examining the relationship between the neural signature response of social exclusion and loneliness outcome can provide insight into the social cognitive aspect of loneliness. Loneliness is defined as perceived social isolation and occurs when we have a mismatch between the social relationships that we have and those we want (Perlman & Peplau, 1981). According to the social cognition framework of loneliness (Figure 1a), lonely individuals have maladaptive social cognition processes that maintain or even aggravate the feeling of loneliness (Cacioppo & Hawkley, 2009). The brains of lonely individuals are on high alert for social threats compared to the non-lonely, so lonely individuals tend to view their social world as threatening and punitive. Specifically, loneliness can trigger implicit hypervigilance for social threats, which in turn produces attentional, confirmatory, and memory biases that may induce more loneliness. This theoretical model emphasizes the social cognitive aspect of loneliness and is supported by some pieces of evidence from behavioral and neuroimaging research (Cacioppo et al., 2009; Cacioppo & Hawkley, 2005). Masi et al. (2011) also found that the greatest effect on loneliness was seen with interventions that addressed maladaptive social cognition, e.g. interventions regarding automatic negative thoughts as faulty hypothesis that need to be verified.

Few studies have attested the effect of loneliness on the perception of social threat yielded from 'social exclusion.' Vanhalst et al. (2015) showed that chronically lonely adolescents were hypersensitive to social exclusion and hyposensitive to social

inclusion. Wesselmann et al. (2012) collected real-time affective response during Cyberball and showed that lonely individuals had slower affective decrease when ostracized but quicker affective increase when included. These inconsistent results on response to social exclusion in lonely individuals emphasize the need to reexamine the relationship between neural reactivity to social exclusion and loneliness.

When lonely individuals experience social exclusion, the cognitions of implicit hypervigilance and negatively biased interpretation of the social world may arise, and these psychological processes may be represented as increased neural reactivity to the exclusion situation. Thus, as illustrated in Figure 1b, identifying the psychological processes during social exclusion, represented by neural reactivity, and their relation to loneliness outcome improves the ecological validity of the neural mechanism model of social exclusion by connecting neural measures to outcomes beyond the lab (Berkman & Falk, 2013).

Figure 1.
Theoretical Background of the Research on Neural Mechanisms of Social Exclusion and Loneliness Outcome



Note. Figure 1a is modified from Cacioppo & Hawkley (2009) and Figure 1b is modified from Berkman & Falk (2013).

1.4 Multivariate pattern analysis of Neural mechanisms

Social and emotional states are neurally represented in distributed patterns across a number of brain regions. Neuronal representations of emotion categories were found to be distributed across a number of cortical and subcortical brain regions based on recent functional neuroimaging studies (Kragel et al., 2015; Saarimaki et al., 2016).

Human and animal research on the effects of social isolation on the brain suggests the involvement of multiple, functionally distinct brain mechanism, including social threat surveillance and aversion (amygdala, anterior insula, anterior cingulate), social reward (ventral striatum), and attention to one's self-preservation in a social context (orbitofrontal cortex, medial prefrontal cortex, superior temporal sulcus, temporal parietal junction) (Cacioppo et al., 2015). Since social exclusion is a subtle, yet complex experience, it can be assumed that various brain mechanisms will be involved in processing and responding to the exclusion situation.

In this study, we implemented multivariate pattern analysis (MVPA) to understand the neural mechanism of social exclusion. Previous studies on social isolation, specifically social exclusion and loneliness, have employed mass-univariate analysis of brain data. This method provides a single summary statistic of the most significantly activated voxel in a brain region (Kragel et al., 2016). It is limited in that it cannot capture the subtle intensity variations within a significant region, lacking sensitivity to subtle spatial patterns in the brain. Also, these models are focused on how well they fit to a particular sample of data and do not examine out-of-sample generalizability of models.

MVPA is an analysis approach that assesses information contained in patterns of brain activity, such as by learning a mapping from multiple voxels to a categorical or continuous variable. MVPA aims to find mental state-specific patterns that emerge

across locally distributed populations of neurons within a region or across neural networks at larger spatial scales (Kragel et al., 2016). These models have higher sensitivity to distributed neural correlates of the underlying representation. Moreover, it takes on error analyses and measures of signal detection theory to check models for generalizability to various samples (Woo & Wager, 2015; Yarkoni et al., 2017). Thus, it may be more appropriate to utilize MVPA in understanding the widely distributed neural mechanisms underlying social exclusion.

1.5 Research Purpose and Hypotheses

This paper aims to identify the neural signature of social exclusion, specifically in older adults, and to examine the individual differences of the signature in relation to self-reported loneliness. First, we will train a model that predicts the social exclusion versus inclusion state from brain activations during exclusion and inclusion condition of Cyberball. In other words, we hypothesize that a MVPA model will identify the neural pattern which distinguishes the brain's exclusion and inclusion state. Second, it is hypothesized that the neural patterns of social exclusion will be widely distributed in the predefined networks, namely the mentalizing network, amygdala network, and social pain network. Lastly, it is hypothesized that the neural pattern response to social exclusion will be associated with individual differences in loneliness.

Chapter 2. Methods

2.1 Participants

Eighty-eight healthy older adults (51 females, Mean age=70.95, S.D. of age=6.46) from the Korean Social Life, Health, and Aging Project (KSHAP) participated in the study. These participants lived in the same neighborhood in a rural area in South Korea. Of the initial 110 participants of the 4th wave of KSHAP, we excluded those with a history of psychiatric or neurological diseases, traumatic brain injury, loss of consciousness following the injury, or mild cognitive impairment, in order to sample normal aging adults. Those who did not comprehend the social exclusion task, showed excessive head motion during the fMRI scan, had vision problems, or were not right handed were additionally excluded.

To control for baseline physiological states of participants, they were instructed to sleep well, be rested, and not exercise, drink or eat anything before the scan. All participants provided written information consent after experimental procedures were described and received an honorarium for their participation. The study was approved by the Seoul National University Institutional Review Board.

Table 1.

Descriptive Statistics of Participant Information

Variable	*n*	%	*M*	*SD*
Gender				
Female	51	58		
Male	37	42		
Age	88	100	70.95	6.46
Years of education	88	100	7.45	6.46
0 – 5y	15	20.50		
6y	42	39.80		
7 – 12y	38	32.90		
12y or more	10	6.70		
Number of chronic diseases [a]	88	100	1.37	1.05
Self-rated health status	88	100	2.98	0.83
Loneliness	88	100	36.50	9.32
Depression	88	100	9.35	6.49
Perceived stress	88	100	12.78	9.67
Anxiety	88	100	1.22	1.62
Extraversion	88	100	25	5.33
Response to exclusion				
Recognized exclusion [b]	88	100	1	0.00
Feeling excluded	88	100	4.80	0.70
Feeling ignored	88	100	1.98	1.50
Feeling hurt (sad)	88	100	1.88	1.50
Average communication with players	88	100	2.76	1.07
Average closeness with players	88	100	1.35	0.94

[a] Chronic diseases included hypertension, diabetes, hyperlipidemia, osteoporosis, cancer, myocardial infarction, angina pectoris, cataract, and glaucoma.

2.2 Social Exclusion Task : Cyberball

In order to induce a situation where participants experience social exclusion, we adapted a modified version of the Cyberball task. In the original task, participants played a virtual-ball tossing game with unknown players online and at some point during the game stopped receiving the ball from other players, perceiving themselves to be excluded (Williams et al., 2000). This experience of social exclusion is known to cause increased negative emotions and higher vulnerability to belonging, control, self-esteem, and meaningful existence (Williams, 2009).

In this study, participants were led to believe that they were playing the Cyberball with participants that came to the MRI center together from their village. Before the task, the three participants that came to the center together were asked what kind of

relationship they have and how long they have known each other (in years). They were also individually asked how frequently they communicate with the others (1=none, 5=everyday) and the extent to which they feel close to the others using the five-point Likert scales (1=don't know, 5=very close). Although the participants lived in the same neighborhood, they had different levels of acquaintance to one another from strangers to close friends or spouse. During the task, participants were instructed to press left or right buttons on a fMRI-compatible response box in order to throw the ball to a player on the left or right.

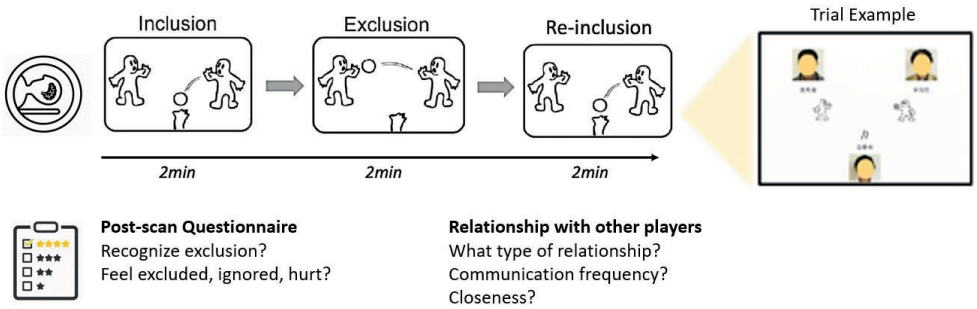
As many of the participants were older adults living in rural areas with fewer years of education, we expected some of them to have difficulties in fully understanding and mentally visualizing the virtual ball-tossing environment. Thus, before the task, participants played a short, face-to-face ball-tossing game with an actual plastic ball and a practice session playing the Cyberball with computers. During the task, participants were expressed as animated characters and given names and faces of the three players next to each character. The participant's character was positioned in the bottom center and the other two players were positioned on the upper left and right in random order (Figure 2).

In reality, participants were tested individually and the throws of other players were controlled by a computer program. The task comprised of three blocks of social interaction. In the inclusion condition, participants were given the ball often throughout the game for 50% of all throws. In the exclusion condition, after a few included throws (i.e. 5 throws), participants were not given the ball at all, thus experiencing social exclusion. In the re-inclusion condition, after a few included throws (i.e. 5 throws), participants were given 100% of throws. Each condition lasted approximately 2 minutes (i.e., total of 6 minutes of 130 throws on average). Brief

random delays of 0.5s-3.5s were inserted before each player made a throw to enhance participants' belief that they were playing with other people.

Figure 2.

Cyberball Paradigm



2.3 Post-scan questionnaires and Loneliness survey

Following the MRI scan, participants rated how they felt about each state of the task (Zadro et al., 2003). They were asked if they recognized that they received less or more tosses in different conditions (yes or no), in order to check if manipulation of ostracism was successful. They also rated on various reactions to the exclusion condition: how much they felt they were excluded, ignored, and hurt (or sad) using five-point Likert scales (1=not at all, 5=very much). As this experiment used deception to induce social exclusion experience, debriefing procedures were administered after the experiment.

Loneliness was measured with the Korean version of the 20-item UCLA-r Loneliness scale (Kim, 1997; Russell, 1980). This scale measured overall perceived loneliness and satisfaction of social relationships. It consisted of 20 items in four-point Likert scales that measure various social and affective aspects of loneliness, without explicitly asking if one 'feels lonely' (e.g. 'I lack companionship,' 'There are people I feel close to,' 'I feel isolated from others,' 'People are around me but

not with me').

We administered additional questionnaires in order to take other factors into account, including the Geriatric Depression Scale (Korean Version) (GDS; Brink et al., 1982; Jung et al., 1997), Geriatric Anxiety Inventory – Short Form (Korean Version) (GAI-SF; Byrne & Pachana et al., 2007), Perceived Stress Scale (Korean Version) (PSS; Baek, 2010; Cohen, Kamarck, and Mermelstein, 1983), Big Five Inventory (Korean Version) (BFI-K; Kim et al., 2010; John, Donahue, & Kentle, 1991), and a health survey about the number of chronic diseases they have and a self-reported health status (1=bad, 5=very good). Chronic diseases included hypertension, diabetes, hyperlipidemia, osteoporosis, cancer, myocardial infarction, angina pectoris, cataract, and glaucoma.

2.4 FMRI acquisition and preprocessing

All MRI data were acquired on a 3T SIEMENS MAGNETOM Trio TIM Syngo MR with 32 channel coil and GRAPPA. Whole-brain fMRI data of 180 volumes were acquired during Cyberball, using echo-planar imaging(EPI) sequence with the following parameters: repetition time (TR)=2000ms, echo time (TE)=30ms, flip angle (FA)=79°, field of view (FOV)=240mm, 30 slices (3x3x4mm^3 voxels) parallel to the anterior commissure-posterior commissure line. Structural data were acquired using a T1-weighted MP-RAGE with the following parameters: TR=23000ms, TE=2.36ms, FA=9°, FOV=256mm, 1x1x1mm^3 voxels. Stimulus presentation and behavioral data acquisition were administered using PsychoPy (Peirce et al., 2019).

Functional images were corrected for differences in slice acquisition timing to the first slice and were motion corrected using SPM12. They were warped to SPM's

normative atlas (East Asian MNI152) using warping parameters estimated from co-registered structural images and interpolated to 2x2x2mm^3 voxels. Images were smoothed with a $6mm$ FWHM Gaussian kernel in order to ameliorate intersubject differences in localization while retaining sensitivity to fine-scale activity patterns. Subjects with excessive head motion (absolute motion > 3, mean motion > 0.5, max motion > 4.5, mean frame-to-frame displacement > 0.15) were excluded from the analysis, resulting in 88 subjects.

Voxel-wise statistical parametric maps for each task condition were estimated using the first-level GLM analysis. For each individual, three task conditions were constructed for regressors of interest, corresponding to 2-min inclusion, exclusion, and reinclusion periods. For each task regressor, a Boxcar function was convolved with SPM12's canonical hemodynamic response function. Also, a set of nuisance covariates were included to capture noise (a constant term for the run and six mean-centered motion parameter estimates) and fixation-cross epoch was not included as a regressor since the model may become over-parameterized. A high-pass filer of 128s was applied to remove low-frequencies from the data. The voxel-wise statistical parametric maps for exclusion and inclusion conditions that were calculated for each subject were used as features in multivariate pattern analysis (MVPA).

To compare with MVPA results, we analyzed traditional encoding models with general linear modeling (GLM) for exclusion and inclusion contrasts, as well as [exclusion > inclusion] and [inclusion > exclusion] contrasts using a predefined mask of social cognition and behavior (Figure 3).

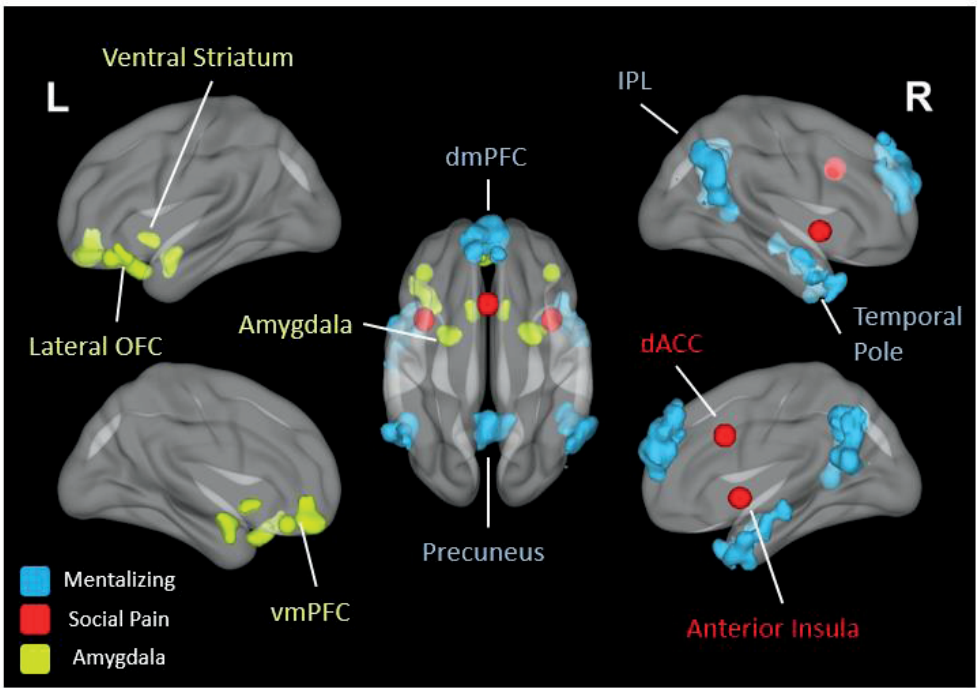
2.5 Multivariate Voxel Pattern Analysis

We used a linear support vector machine (SVM) to train a multivariate pattern classifier that predicts exclusion or inclusion conditions from brain activations. Linear classifiers are advantageous as they are simple with comparable estimation accuracy (Misaki et al., 2010) and are appropriate for analyzing brain data as they combine information from different measurement channels in a weighted sum, which resembles the working principle of neurons (Kriegeskorte, 2011).

First, we selected features with *a priori* maps of functional networks related to social cognition and behavior, which may be closely involved in social isolation based on previous literature (Figure 3). The mentalizing network, including the dorsomedial prefrontal cortex, inferior parietal lobe, temporal pole, and precuneus, was defined from voxels associated with 'mentalizing' term based on meta-analytic database Neurosynth (Yarkoni et al., 2011; https://neurosynth.org/). The amygdala network included the amygdala defined from AAL2, ventral striatum from Harvard-Oxford atlas, lateral orbitofrontal cortex from coordinates used in Bickart et al. (2012), and ventromedial prefrontal cortex from Neurosynth. The social pain network consisted of the dorsal anterior cingulate and bilateral anterior insula extracted from 8-mm-radius spheres around coordinates of peak voxels in "social* & pain*" Neurosynth maps used in Schmälzle et al. (2017). The three networks included 4594 voxels, 1636 voxels, and 343 voxels each and, thus comprised a total of 6573 voxels.

Figure 3.

A Priori Maps of Three Functional Networks related to Social Cognition and Behavior



Note. Feature selection with a priori maps of three functional networks related to social cognition and behavior: mentalizing network, amygdala network, social pain network. Lateral OFC (lateral orbitofrontal cortex, vmPFC (ventromedial prefrontal cortex), dmPFC (dorsomedial prefrontal cortex), IPL (inferior parietal lobe), dACC (dorsal anterior cingulate)

Then, SVM classifier with a linear kernel, L2-regularization parameter C=1.0, and hinge loss function was implemented using scikit-learn (based on libsvm). SVM is a supervised learning, binary classifier that finds a hyperplane that separates two different classes of data points by the largest distance. The algorithm depends on the data only through dot products ($h(x) = g(\omega^T x + b)$, where g is the sign determining class) and finds the hyperplane with maximum margin while minimizing margin errors (soft-margin). SVM is widely used in bioinformatics and other disciplines due to its high accuracy, ability to deal with high-dimensional data, and flexibility in modeling diverse sources of data (Schölkopf et al., 2004).

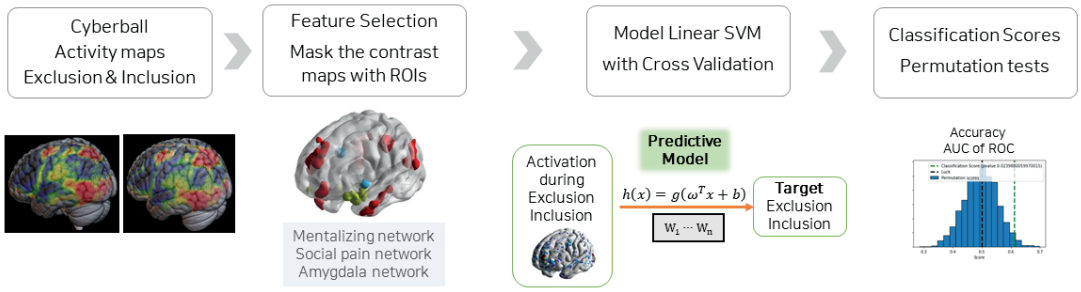
The pattern classifier was trained on first-level contrast images for exclusion and

inclusion conditions. Leave-one-subject-out cross-validation was implemented where training was performed with n-1 subjects and testing was then applied to one remaining subject, and repeated across all subjects. This procedure allows the model to estimate whether the neural signatures of social exclusion are consistent across individuals. Voxel activation values were normalized during cross validation to ensure independence between training and test datasets. The classification score was defined as the accuracy score and the area under the Receiver Operating Characteristic (ROC) curve (AUC) which was averaged across cross-validation folds.

To test whether classification scores exceeded chance level, a chance-level performance percentage was derived as a ratio of 1 over the number of categories, thus 50% in this study. Also, permutation tests were conducted to simulate the probability distribution of the classification and thus provided confidence limits of the chance-level accuracies. Each permutation step included shuffling of condition labels and rerunning the classification with cross-validation, repeated 5000 times. After testing classification scores of the model, further interpretation and analysis were administered on a model that was trained on the full sample. Figure 4 illustrates the overall procedure of MVPA used in this study.

Figure 4.

Multivariate Pattern Analysis Procedure



Note. Multivariate pattern analysis was conducted with the following steps. 1) First-level contrast maps of exclusion and inclusion conditions were estimated for each subject, 2) Voxels within an a priori mask of three functional networks related to social cognition and behavior were selected, 3) Linear SVM was trained with leave-one-subject-out cross-validation using the masked contrast maps of exclusion and inclusion, 4) Permutation tests were used to validate the classification score of the model.

2.6 Feature Importance Analysis

Once the model predicting social exclusion condition has been trained, it is important to interpret the model, i.e. identify which voxel or region features are most predictive of the outcome. The desired goals of brain decoding models are to first predict the state with neural responses and then to determine specific regions that contain relatively more information about the predicted state.

Unlike encoding models whose parameters indicate how external variables are encoded in the brain data, parameters (weights) of decoding models cannot be directly interpreted because those weights depend not only on brain activity of interest but also on noise components in the data (Haufe et al., 2014). Thus, feature importance can be an alternative method for parameter interpretation when employing multivariate pattern analysis to understand neural mechanisms of psychological states.

One common, reasonably efficient, and reliable technique is permutation feature

importance. Permutation feature importance is the percent increase in prediction error (1-AUC) after a feature's value is permuted, which breaks the relationship between the feature and the true outcome (Altmann et al., 2010; Breiman 2001; Fisher et al., 2018) Another feature importance technique is the drop-column, or "lesioned", feature importance. It is the percent increase in prediction error after a feature is removed from the model (Whelan et al., 2014). For both importance metrics, higher values indicate that the feature has higher relative importance to the prediction and values of 0 or less indicate that the feature is not important to the prediction.

We calculated permutation feature importance and lesioned feature importance at the voxel-level, region-level, and network-level. Voxels were grouped together as regions and networks to calculate feature importance at the region-level and network-level.

2.7 Quantifying the Neural Signature Response to Social Exclusion

In order to examine the loneliness-related individual differences in neural sensitivity to social exclusion, the level of pattern response was calculated by taking the dot product of the pattern weights ($\vec{w}$) and vectorized activation contrast maps for each condition ($\vec{x}$), i.e. ($\vec{w} \cdot x$). This yields a scalar value that is the weighted average of activation for each subject in each condition, representing the expression of the pattern in response to exclusion or inclusion state (Wager et al., 2013; Lada et al., 2020).

We examined the level of pattern response during exclusion and inclusion of each subject and its association with individual differences in loneliness. Pearson's correlation analysis was conducted to examine the trend of associations between

pattern responses and loneliness. Then, multiple regression analyses predicting loneliness with pattern responses were administered, controlling for basic demographic factors (gender, age, education, health status) and task-related contextual factors (average communication frequency and closeness with two other players). Finally, we tested whether the relationships between loneliness and pattern responses during exclusion versus inclusion were significantly different. We first compared the correlation coefficients *r* of loneliness and pattern responses during exclusion versus inclusion, via one-tailed Steiger's Z test (Meng et al., 1992). Then, using the Potthoff analysis (Potthoff, 1966), we created a dummy variable to code the exclusion/inclusion conditions and included the interaction between the dummy variable and pattern responses as a predictor in a multiple regression predicting loneliness. The significance of the interaction term would indicate that the regression coefficients of pattern responses during exclusion and inclusion were significantly different.

In addition, network-level pattern response can be calculated by taking the dot product of pattern weights of a particular network and its corresponding voxel activations. We calculated separate pattern responses for the three functional networks, mentalizing network, amygdala network, and social pain network, and examined their correlations with loneliness. If the network-level patterns of social exclusion show individual associations with loneliness, it may be suggested that certain networks are relatively more related to loneliness and, thus, the neural patterns of social exclusion are organized in a modular rather than an integrated fashion. It may also indicate that certain brain functions are employed more than other functions when experiencing social exclusion in lonely adults.

To examine whether pattern responses were related to factors other than loneliness,

correlation analyses were conducted with behavioral responses to exclusion, contextual factors related to the Cyberball, and other psychological variables. In order to show that the relationship with other players of the Cyberball was not the driving factor of neural responses to social exclusion, we tested whether it had moderation effects on the relationship between pattern response and loneliness.

Chapter 3. Results

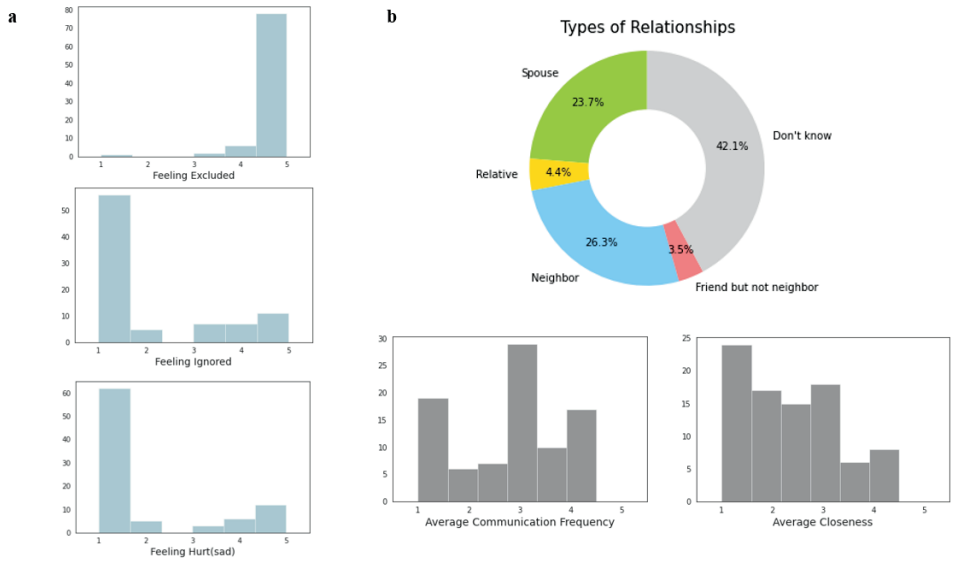
3.1 Behavioral results

Behavioral results confirmed that all participants recognized that they received less ball tosses during the exclusion condition of the Cyberball, indicating successful manipulation of ostracism. (Figure 5a) Most participants felt excluded from other players during the exclusion condition (96.6% reported over 4), whereas only a subset of them felt ignored (70.9% reported 2 or less) or hurt(sad) (76.2% reported 2 or less).

As shown in Figure 5b, of all the relationships that participants had with other players, 42.1% of participants did not know each other, 29.9% were neighbors or friends, and 28.1% were spouses or relatives. Additional information on the duration of relationship, communication frequency, and closeness with other players can be found in Supplementary Figure S1. The average frequency of communication and the average feeling of closeness with the two other players represents the contextual factors that contribute to the specific instance of social exclusion. Indeed, variances in social relationships of people we interact with may effect one's response to being socially excluded from them and one's overall feeling of loneliness (Wirth & Williams, 2009). As this study mainly focuses on the general situation of social exclusion and its association with loneliness, the relationships with other players of the task were controlled for in later analysis. Nevertheless, we provided preliminary analysis of the effects of contextual factors on neural sensitivity to social exclusion and loneliness.

Figure 5.

Task-related Variables



Note. (a) Behavioral responses to the social exclusion task. (b) Relationships with two other players of the task.

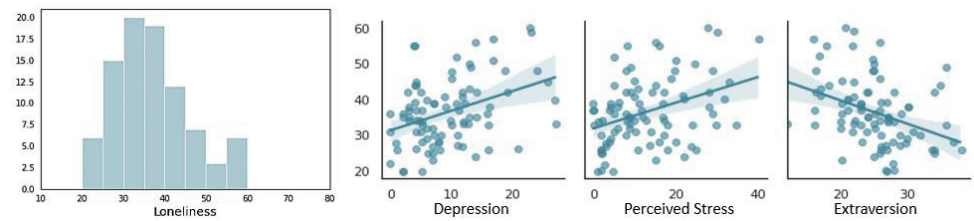
As shown in Table 1 and Figure 6, participants reported different levels of loneliness in life (Mean=36.5, S.D.=9.32). Loneliness was positively correlated with other psychological states/traits such as depression (r=.383, p<.01) and perceived stress (r=.373, p<.01), negatively correlated with extraversion personality (r=-.372, p<.01), but was not related to age, education or physical health. In line with previous findings, loneliness can be considered a psychological state that consists of social and emotional aspects that are related to but distinct from other states or traits such as depression, anxiety, and perceived stress (Cacioppo et al., 2000; Cacioppo et al., 2010; Domènech-Abella, 2019). In addition, loneliness was positively correlated with feeling hurt in response to the social exclusion task (r=.239, p<.05) and was not related to average frequency of communication or the average feeling of closeness with other players of the task. Considering that lonely individuals reported stronger behavioral responses to social exclusion, we can anticipate individual differences

related to loneliness in the neural sensitivity to social exclusion, which seem to be independent from situational factors such as relationships with other players of the task.

Figure 6.

Loneliness and its Relation to Other Variables

a



b

	Age	*Self-reported Health*	*Num of Chronic diseases*	*Depression*	*Perceived stress*	*Extraversion Personality*	*Feeling Hurt*	*Average Communication with players*	*Average Closeness with players*
Corr	-.006	-.163	-.207	.383**	.373**	-.372**	.239*†	-.110	-.144
p	.954	.128	.053	.000	.000	.000	.025	.309	.181

*p<.05, **p<.01, †Spearman's correlation

Note. (a) Histogram of loneliness and scatterplot of its relation with other variables. (b) Correlation between loneliness and other variables, including age, health status (self-reported heath, number of chronic diseases), depression, perceived stress, extraversion personality, and task-related variables (feeling hurt response, average communication and closeness with other players).

3.2 FMRI Pattern Signature

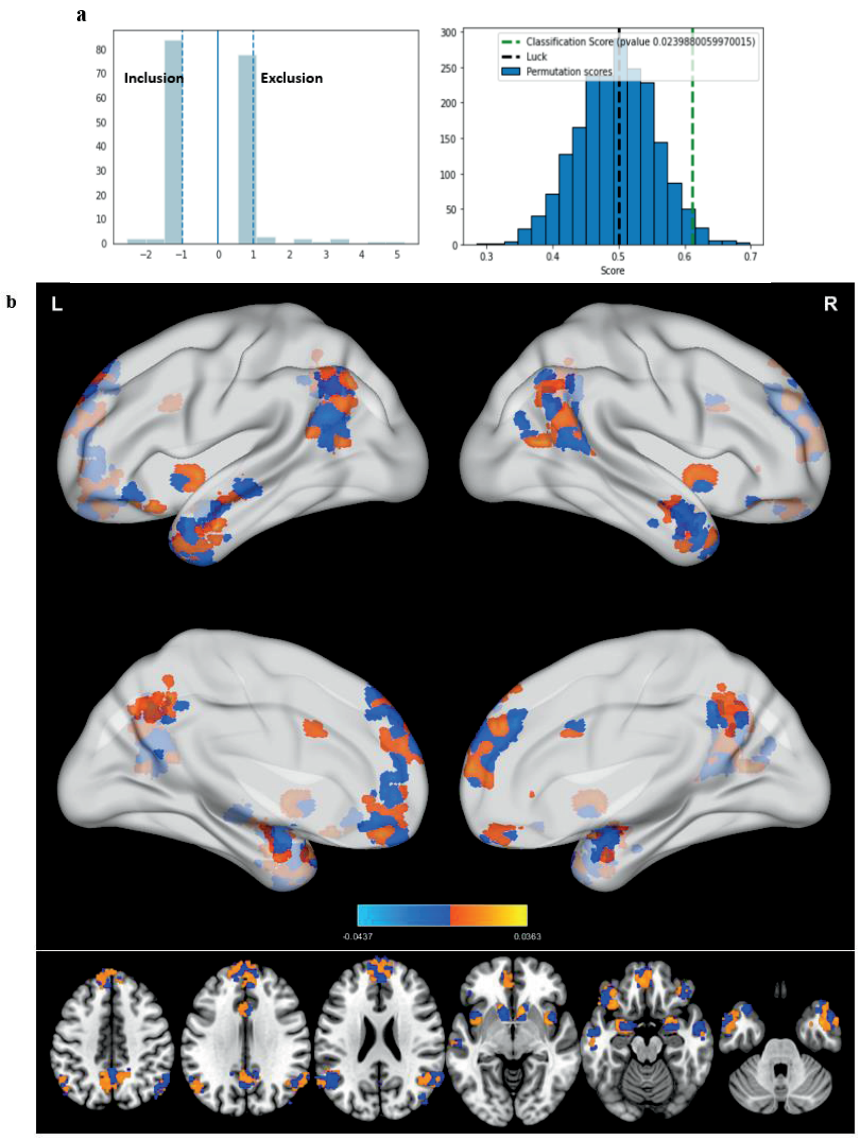
The linear SVM classifier discriminated social exclusion and inclusion with an accuracy of 0.632 (95% CI: [0.576, 0.685]) and AUC of ROC curve of 0.693 (95% CI: [0.595, 0.791]). The classification scores were significantly above chance level (chance level 0.5, permutation significance $p < .05$) (Figure 7a).

The regions with the highest peak voxel weights included the bilateral IPL, temporal pole (positive weights), amygdala, and ventral striatum (negative weights), belonging to the mentalizing network and the amygdala network. Within each region, some regions had more positive weights (bilateral anterior insula, dACC, precuneus,

vmPFC) and some had more negative weights (left ventral striatum, left lateral OFC, right temporal pole, left IPL). Other regions, including the bilateral amygdala, right lateral OFC, right ventral striatum, dmPFC, right IPL, and left temporal pole, consisted of similar numbers of positive and negative weights, indicating locally distributed patterns of weights within those regions (Figure 7b).

Figure 7.

Linear SVM Classification Results



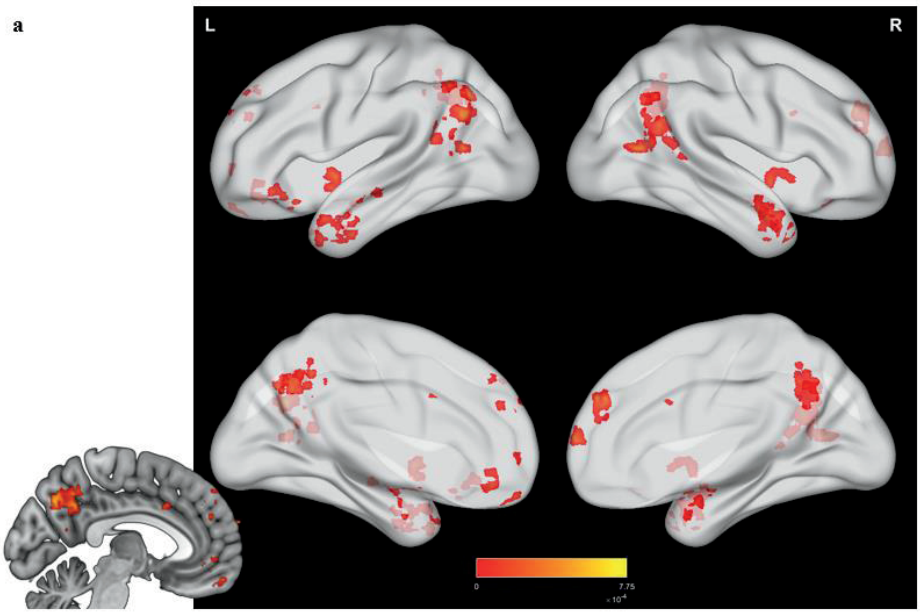
Note. (a) Histogram of projections training separation from the decision boundary and histogram of permutation scores. (b) Pattern weight map, unthresholded for visualization

In order to identify features that were most important to the prediction, we calculated voxel-level, region-level, and network-level feature importance via permutation and "lesioning." Voxel-level permutation feature importance showed that 1704 out of 6573 voxels (26%) had positive importance values and thus contributed to the prediction (Figure 8a). The regions with voxels of the highest importance were the precuneus, dmPFC, right temporal pole, bilateral IPL, left amygdala, vmPFC, right ventral striatum, and left anterior insula. According to region-level feature importance analysis (Figure 8b), the most important regions of the prediction that were commonly ranked highest for both measures of feature importance were dmPFC, left ventral striatum, right temporal pole, right IPL, precuneus, and the left amygdala. These regions are part of the mentalizing network (dmPFC, right temporal pole, right IPL, precuneus), amygdala network (left ventral striatum, left amygdala), and social pain network (right anterior insula). These results were consistent with network-level feature importance analysis with the mentalizing network ranking highest importance followed by the amygdala network and then the social pain network. Although importance scores were correlated with the number of voxels (Spearman's correlation for permutation importance $r=.717$, $p=.002$, lesioned importance $r=-.150$, $p>.100$), the regions that were commonly ranked important by the two measures included very small-sized regions, e.g. the left ventral striatum (107 voxels) and left amygdala (220 voxels).

Figure 8.

Permutation and Lesioned Feature Importance Analysis

a



b

Regions	Permutation Feature Importance	No. of Voxels
dmPFC	0.119	1327
Right Temporal Pole	0.057	431
Right IPL	0.051	902
Precuneus	0.040	663
Left IPL	0.028	681
Left Temporal Pole	0.023	590
Left Ventral Striatum	0.023	107
Left Lateral OFC	0.012	432
vmPFC	0.011	422
Right Anterior Insula	0.011	110
Left Amygdala	0.006	220
dACC	0.006	123
Left Anterior Insula	0.006	110
Right Lateral OFC	0	123
Right Amygdala	0	248
Right Ventral Striatum	0	84

Regions	Lesioned Feature Importance	No. of Voxels
dmPFC	0.113	1327
Left Amygdala	0.034	220
Right Lateral OFC	0.023	123
Left Ventral Striatum	0.023	107
Right Anterior Insula	0.023	110
Right Ventral Striatum	0.011	84
Right IPL	0.011	902
Precuneus	0.011	663
Right Temporal Pole	0.011	431
Right Amygdala	0	248
Left Anterior Insula	-0.012	110
vmPFC	-0.023	422
Left Temporal Pole	-0.023	590
Left IPL	-0.034	681
dACC	-0.034	123
Left Lateral OFC	-0.057	432

Networks	Permutation Feature Importance	No. of Voxels
Mentalizing network	0.414773	4594
Amygdala network	0.221591	1636
Social pain network	0.073864	343

Networks	Lesioned Feature Importance	No. of Voxels
Mentalizing network	0.125	4594
Amygdala network	0.045	1636
Social pain network	0.023	343

Note. (a) Map of voxel-level permutation feature importance. (b) Region-level and network-level feature importance values (permutation and lesioned importance) in descending order and the number of voxels within each region.

In comparison, GLM results showed some commonly overlapping regions involved in exclusion and inclusion conditions, as well as some regions that involved differently in the two conditions. The bilateral middle temporal gyrus (inferior parietal lobe, IPL) and precuneus were activated in both exclusion and inclusion conditions. The bilateral anterior insula and lateral orbitofrontal cortex (OFC) were additionally activated in the inclusion condition. The [inclusion>exclusion] contrast map showed that dorsomedial prefrontal cortex (dmPFC), temporal pole, ventromedial prefrontal cortex (vmPFC), precuneus, IPL, ventral striatum, and lateral OFC were highly activated during inclusion than exclusion. In the [exclusion>inclusion] contrast which was analyzed at the whole-brain level, regions around the 4th ventricle and bilateral inferior occipital gyrus were activated more during exclusion than inclusion (Supplementary Figure S2).

3.3 Neural Signature Response to Social Exclusion and its relationship with Loneliness

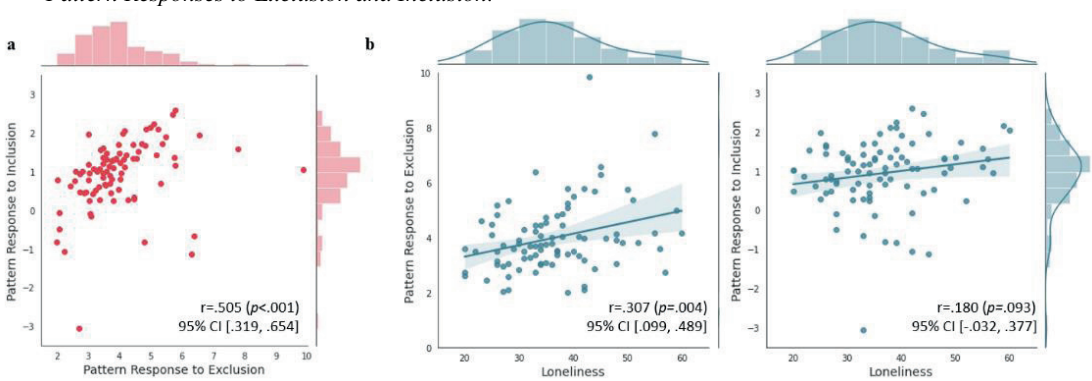
Pattern responses during exclusion and inclusion were calculated for each subject. Individuals with higher pattern response in the exclusion condition showed higher response in the inclusion condition (Spearman's correlation $r=.505$, $p<.001$) (Figure 9a). As in Figure 9b and 9c, whole-brain pattern response during the exclusion condition was positively correlated with loneliness (Pearson's correlation $r=.307$, $p=.004$). Multiple regression predicting loneliness with pattern response during exclusion showed that the model significantly explained 15.4% of the variance ($R^2=.154$, $F(6,81)=2.45$, $p=.031$) and the pattern response during exclusion contributed significantly to the prediction of loneliness (Beta=2.073, $t=2.719$, $p=.008$), after controlling for gender, age, education, health status, and average

closeness or communication with other players. The level of pattern response during the inclusion condition was not significantly correlated with loneliness (Pearson's correlation r=.180, p=.093). In terms of coefficients, the correlation with loneliness was not significantly greater for pattern response during exclusion than for pattern response during inclusion (z=1.223, p=.111). Multiple regression predicting loneliness with pattern expression during inclusion showed that the model did not significantly explain the variance (R^2=.100, F(6,81)=1.492, p=.191) and the pattern expression during inclusion did not predict loneliness (Beta=1.633, t=1.444, p=.153), after controlling for the same variables. As in Figure 9d, although the regression model with the interaction term 'pattern response x conditions' significantly explained loneliness (R^2=.0632, F(3,172)=3.866, p=.01), the regression coefficients of pattern responses during exclusion and inclusion were not significantly different (Beta=.168, t=.249, p=.804).

Of the 88 subjects, there were two outliers of pattern response to exclusion and inclusion. We found similar results when administering the identical analyses after removing the outliers: pattern response to exclusion showed positive correlations with loneliness (r=.311, p=.003) and pattern response to inclusion did not have significant correlations with loneliness (r=.184, p=.088).

Figure9.

Pattern Responses to Exclusion and Inclusion.



c

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**36.789**	**11.812**	**3.114**	**0.003**	**13.286**	**60.292**
Gender	0.368	2.118	0.174	0.863	-3.846	4.581
Age	-0.028	0.152	-0.181	0.856	-0.331	0.275
Education	-0.080	0.244	-0.329	0.743	-0.565	0.405
No. of chronic diseases	**-1.935**	**0.926**	**-2.089**	**0.040**	**-3.777**	**-0.092**
Average closeness	-1.373	1.050	-1.308	0.195	-3.463	0.717
Pattern response during exclusion	**2.073**	**0.762**	**2.719**	**0.008**	**0.556**	**3.590**

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**42.647**	**11.910**	**3.581**	**0.001**	**18.950**	**66.343**
Gender	0.642	2.181	0.294	0.769	-3.697	4.981
Age	-0.001	0.157	-0.008	0.993	-0.313	0.311
Education	-0.119	0.252	-0.471	0.639	-0.620	0.383
No. of chronic diseases	-1.897	0.958	-1.980	0.051	-3.804	0.010
Average closeness	-1.746	1.071	-1.631	0.107	-3.877	0.385
Pattern response during inclusion	1.634	1.131	1.444	0.153	-0.617	3.884

d

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**31.125**	**1.750**	**17.787**	**0.000**	**27.671**	**34.579**
Pattern response	**-3.582**	**-2.047**	**-2.047**	**0.042**	**-7.036**	**-0.127**
Conditions	**2.077**	**3.087**	**3.087**	**0.002**	**0.749**	**3.406**
Pattern response x Conditions	0.168	0.249	0.249	0.804	-1.161	1.496

Note. (a) Scatterplot of pattern expressions during exclusion and inclusion. (b) Scatterplot regression line of whole-brain pattern expression and loneliness. (c) Multiple regression results predicting loneliness from whole-brain pattern expressions. (d) Multiple regression with interaction term 'pattern response x conditions' testing whether the coefficients of pattern responses during exclusion and inclusion are significantly different.

We also investigated whether pattern response in certain functional networks predict loneliness better than others. By calculating pattern expression within voxels consisting each network, we examined the relationship of pattern expression in three functional networks (mentalizing network, amygdala network, social pain network) with loneliness. None of the individual pattern expression of networks during exclusion and inclusion were associated with loneliness (Supplementary Table S1).

Additionally, pattern expressions during exclusion and inclusion were not different between individuals who reported stronger behavioral response to social exclusion, i.e. feeling excluded, ignored or hurt. They were also not related to the contextual factors of the task, i.e. average communication or closeness with other players. These contextual factors of the task did not moderate the relationship between pattern responses and loneliness. Finally, they were not associated with other psychological states, such as depression, perceived stress, anxiety, or extraversion personality (Supplementary Table S2).

Chapter 4. Discussion

Social isolation is an important risk factor to the health of older adults and understanding the psychological and neurophysiological processes that regulate the feeling of loneliness is an essential step towards developing effective interventions for loneliness. Social exclusion is a specific incident of social isolation that can induce different levels of reactivity to social cues and may be related to the general feeling of loneliness. In this study, we aimed to understand the neural mechanisms of social exclusion using MVPA and their individual differences related to loneliness.

We identified a neural pattern signature of social exclusion in older adults based on fMRI responses to exclusion and inclusion during Cyberball task. This pattern discriminates social exclusion from inclusion with 0.632 accuracy and 0.693 AUC. The regions with the highest peak voxel weights include the bilateral IPL and temporal pole of the mentalizing network, and amygdala and ventral striatum of the amygdala network. Feature importance analysis showed that the regions contributing most to the prediction were the dmPFC, right temporal pole, right IPL, and precuneus of the mentalizing network, left amygdala and left ventral striatum of the amygdala network, and right anterior insula of the social pain network. Thus, primarily the regions of the mentalizing and amygdala network play important roles as the neural mechanisms of social exclusion. These results may imply that psychological functions related to these regions are involved during social exclusion experience.

The regions of the mentalizing network, including IPL, temporal pole, dmPFC, and precuneus, are related to the ability to infer one's own and others' state of mind. During social exclusion, these regions may support the process of considering intentions of the individuals who are excluding the participant in the social event or

the process of internal ruminations about the relevance of potential ongoing exclusion for broader social relations (Amodio & Frith, 2006; Schmälzle et al., 2017). The amygdala network, including the amygdala, lateral OFC, ventral striatum, and vmPFC, is related to various social relationship characteristics and emotional values. The amygdala is considered the hub of the social brain, sharing anatomical and functional connections with almost every other brain region implicated in social cognition. The vmPFC and ventral striatum is involved in processes related to motivating prosocial or affiliative behaviors. Lateral OFC supports perception and sensory processes involved in detecting, decoding, and interpreting social signals from others in the context of past experience and current goals (Bickart et al., 2014). These regions also support the function of processing affective value and motivational significance of various stimuli, including other people (Zerubavel et al., 2015).

In this study, the social pain network consisting dACC and anterior insula contributed relatively less to the prediction of social exclusion in this study. This network is identified to be associated with distress during exclusion (Eisenberger et al., 2003; Rotge et al., 2015). These differing findings may reflect differences in methodology. The role of dACC in social cognition has mainly been studied via analyses of single univariate activation effects and these studies have shown rather inconsistent results (Cacioppo et al., 2013). However, it is also possible that the subtle experience of being ignored by others may not have been such a strong painful experience for our participants, thus eliciting less involvement of distress functions. In fact, our participants did not report strong negative reactions to being excluded (i.e. feeling ignored, feeling hurt) during the virtual ball-tossing task, which may be attributed to the fact that many of them were older adults (mean age of 71) living in

rural neighborhoods with relatively few years of education. The participants may have processed and responded to the experience of social exclusion to a subtle degree such that neural systems involved in distress as well as behavioral responses of distress were not elicited. It has also been suggested by some studies that regions of the social pain network (dACC and anterior insula) are commonly involved in processing social exclusion and inclusion (Dalgleish et al., 2016; Simard et al., 2018), in which case activations in these regions may not contribute to distinguishing the two conditions.

These results are compatible with another study using MVPA analysis on identifying the neural mechanism of social rejection (Woo et al., 2014). The study found that an fMRI classifier distinguishing ex-partner versus friend was supported by increased activity in mentalizing network regions (dmPFC, right temporal parietal junction(TPJ), precuneus) and other regions associated with negative emotion and its regulation (thalamus, supplementary motor area, inferior frontal gyrus). In our study, we also found the contribution of mentalizing regions to the prediction of social exclusion, and additionally found that amygdala network regions were important. Indeed, social rejection induced by thinking about a break-up experience with one's ex-partner is different from social exclusion during Cyberball, and thus different types of social situations may involve different brain mechanisms. However, it is notable that regions of the mentalizing network have been commonly associated in the studies, suggesting that the mentalizing function is a non-negligible factor of social isolation.

Examining loneliness-related individual differences in pattern response showed that lonely individual had higher pattern response to social exclusion but not inclusion. Previous studies on social cognitive factors of loneliness have indicated

that loneliness can trigger implicit hypervigilance for social threats, which in turn produces attentional, confirmatory, and memory biases (Cacioppo & Hawkley, 2009). The increased neural reactivity to social exclusion in lonely adults may represent hyper-sensitivity to social situations that as perceived as threats to one's social connectedness. The neural responses may capture sensitivity to social exclusion that was not explicitly manifested as behavioral responses. When examining the specificity of the neural response, individual network-level pattern responses during exclusion and inclusion were not related to loneliness. In other words, not the contribution of one specific functional network was enough to predict loneliness. This result indicates that the integration of three distinct functional networks as a whole is important in predicting the loneliness outcome, confirming the previous assumption that neural patterns of social isolation are widely distributed in the brain (Kragel et al., 2015; Saarimaki et al., 2016). Finally, neural pattern responses to social exclusion was not associated with behavioral responses to exclusion (i.e. feeling excluded, ignored, hurt), contextual factors of exclusion (i.e. relationships with other players), and other psychological states (i.e. depression, anxiety, perceived stress). These results demonstrate that the neural signature response to social exclusion is specific to the feeling of loneliness.

The results of the current study have theoretical and practical implications. To our knowledge, this is the first study to investigate the neural mechanisms of social exclusion using MVPA to attain the distributed neural patterns representing complex psychological processes underlying a subtle incident of social isolation, i.e. social exclusion. Also, the importance of the mentalizing network and amygdala network as neural mechanisms of social exclusion suggests that the ability to deduce the mental states of self and others along with the sensitivity to social and emotional

values supports the experience of social exclusion. The results that lonely adults exhibit higher neural reactivity to social exclusion provide evidence to the social cognition framework of loneliness (Cacioppo & Hawkley, 2009). This line of basic research may be informative for developing interventions for chronically lonely adults, such as cognitive behavioral therapy tackling maladaptive social cognition that begets hyper-reactivity to social threats (Masi et al., 2011).

Several limitations should be noted. As the development of decoding models is an ongoing process, models with higher classification performance needs to be developed and generalizability of the identified signature must be attested on other samples of older adults. Also, further investigation on the chronicity of loneliness can provide stronger support for the social cognition framework of loneliness. Although we found no relationships between the neural signature response and behavioral responses to social exclusion, other measures of behavioral responses must be further explored, e.g. other emotional responses, self-preservation tendency, or memory biases of the negative aspects of the situation. Moreover, the currently identified pattern signature consists of *a priori* regions that are known to be related to social cognition and behavior, especially social isolation. As other brain regions with various functions that are yet known to be related may also play part in processing the social exclusion experience, we need to compare the current model with models including other regions of the brain. Finally, the identified pattern signature captures the overall brain mechanisms of social exclusion and does not take into account the effect of contextual factors (i.e. relationships with players). It remains future work to examine the differences in pattern reactivity related to the specific situational characteristics of social exclusion.

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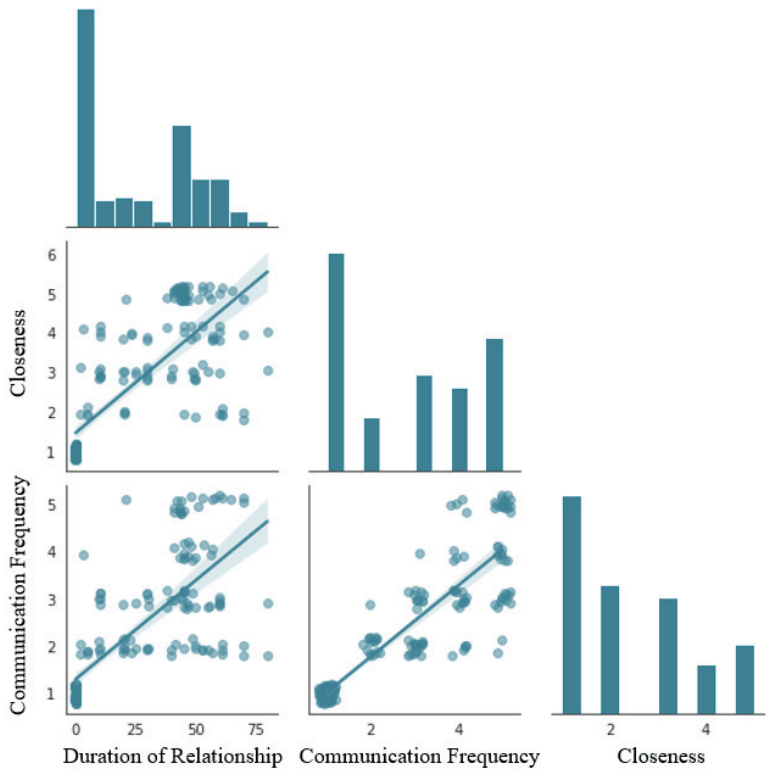
Appendix

Supplementary Figures and Tables

Figure S1.

Relationships with Two Other Players of the Cyberball.

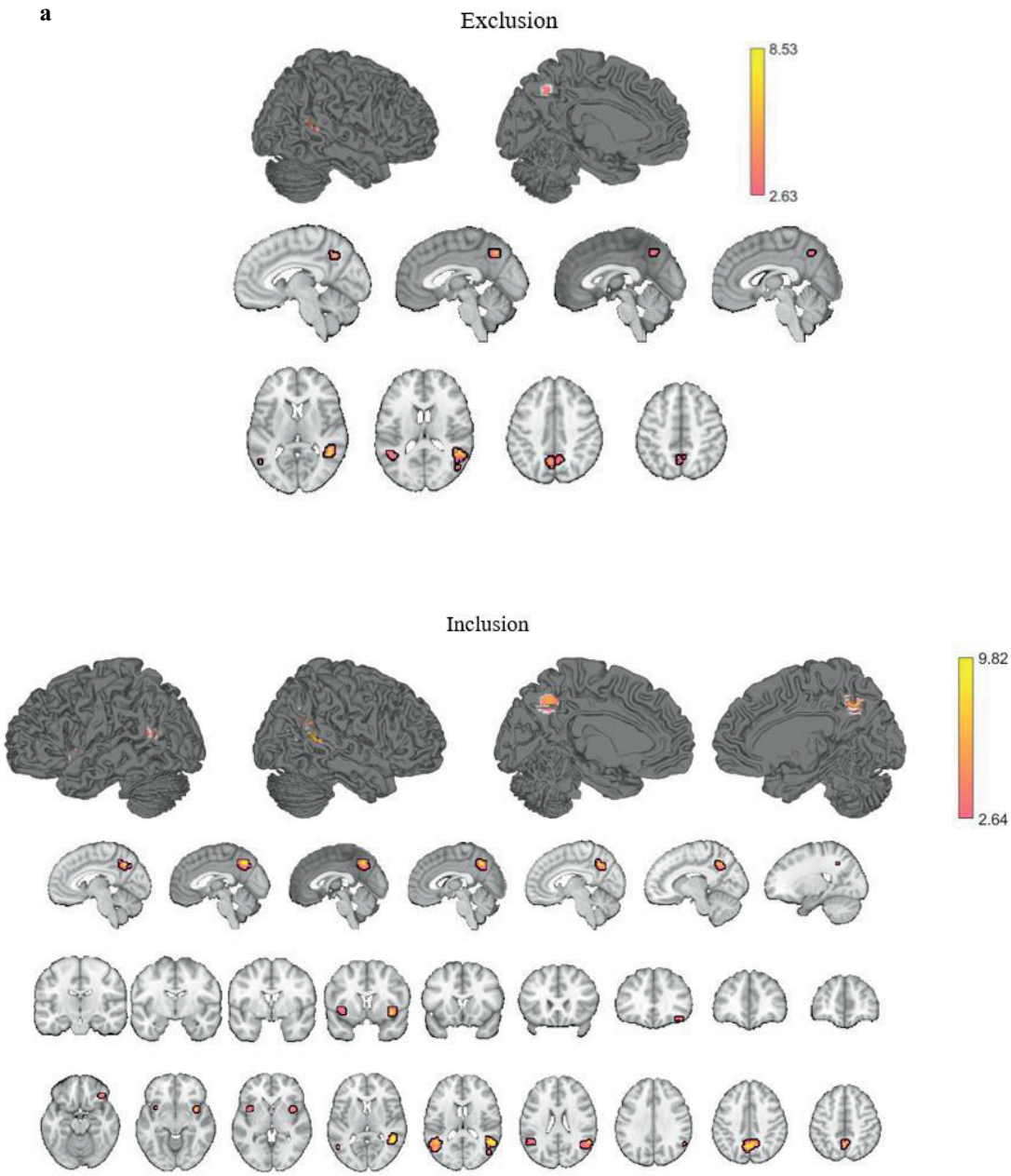


Note. The diagonal figures are histograms of each variable and other figures are scatterplots of each pair of variables.

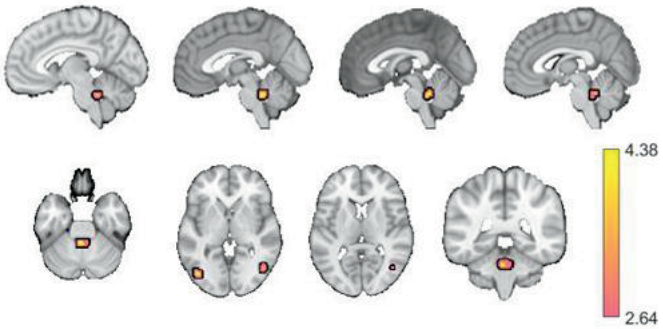
Figure S2.

Group-level analysis of brain activations during the Cyberball

a



Exclusion > Inclusion



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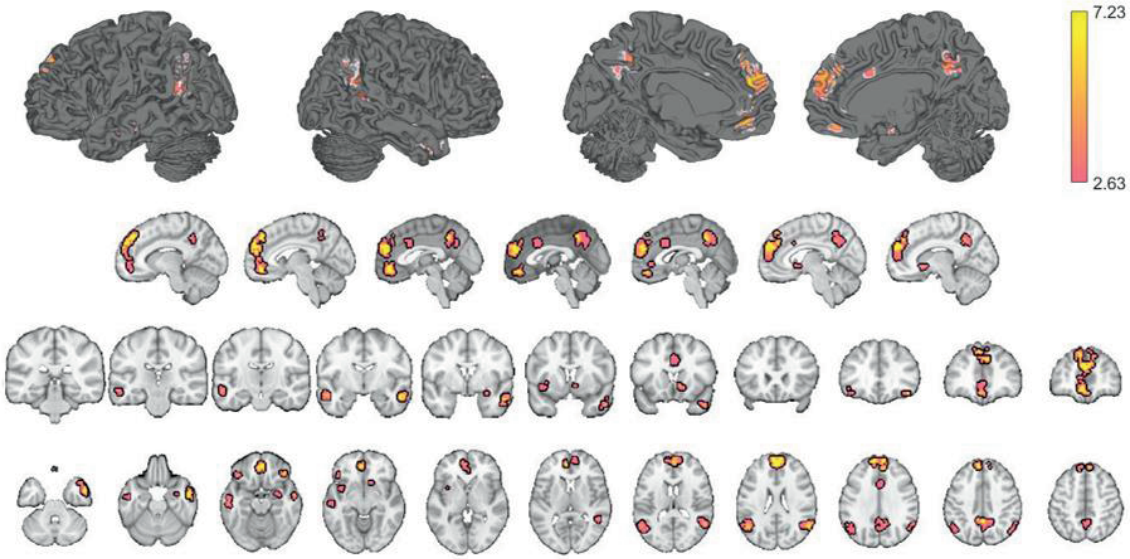

b Contrast	Region	Cluster size	MNI Coordinates			Peak T-score
			x	y	z	
Exclusion	Middle temporal gyrus (R) Inferior occipital gyrus (R) Middle occipital gyrus (R) Angular gyrus (R)	295	50	-64	10	8.53
	Precuneus (L, R)	119	-4	-64	44	4.96
	Middle temporal gyrus (L) Angular gyrus (L)	64	-46	-60	10	4.70
Inclusion	Middle temporal gyrus (R) Inferior occipital gyrus (R) Middle occipital gyrus (R) Angular gyrus (R)	511	50	-64	10	9.82
	Precuneus (L, R)	390	8	-56	44	7.42
	Middle temporal gyrus (L) Angular gyrus (L) Middle, inferior occipital gyrus (L)	290	-50	62	12	7.32
	Anterior insula (R) Posterior insula (R) Putamen (R)	99	36	10	-8	6.58
	Anterior insula (L) Frontal operculum (L)	54	-36	12	-6	4.02
	Lateral, posterior orbital gyrus (R) Inferior frontal gyrus (orbital part) (R)	26	38	34	-12	5.48
Exclusion > Inclusion	4th Ventricle Brain stem Cerebellum (L)	82	-2	-44	-28	4.38
	Inferior occipital gyrus (L) Middle temporal gyrus (L)	65	-42	-74	0	3.93
	Inferior occipital gyrus (R) Middle temporal gyrus (R)	44	46	-68	2	3.44
Inclusion > Exclusion	Superior frontal gyrus medial segment (L, R)	1039	-2	40	44	7.23
	Superior frontal gyrus (L)	31	10	44	44	5.65
	Middle Temporal Gyrus (R) Superior temporal gyrus (R)	245	52	-4	-22	6.76
	Medial frontal cortex (L, R) Anterior cingulate (L)	241	-6	44	-12	5.94
	Precuneus (L, R) Posterior cingulate (L, R)	449	-2	-46	40	5.91
	Angular gyrus (R) Middle occipital gyrus (R)	503	54	-60	26	5.24
	Caudate (R) Lateral ventricle (R) Accumbens (R)	40	8	16	-2	5.19
	Lateral, posterior orbital gyrus (R) Inferior frontal gyrus (orbital part) (R)	29	42	34	-14	5.14
	Inferior frontal gyrus (L) Lateral orbital gyrus (L)	31	-44	34	-8	4.71

Note. (a) The contrast maps of Exclusion, Inclusion, Exclusion>Inclusion, Inclusion>Exclusion conditions using the standard General Linear Model (GLM) analysis across all participants (n=88), thresholded at p<.005 (uncorrected, cluster size>20), as suggested by Lieberman & Cunningham (2009). All maps were masked by the *a priori* mask of social cognition and behavior, except for the [exclusion>inclusion] contrast which was analyzed at the whole-brain level. (b) Regions from the contrasts with the same thresholds.

Table S1.

Correlations between Network-level Pattern Responses and Loneliness.

Network-level Pattern Response		r	*p*
Mentalizing network	Exclusion	-.033	.763
	Inclusion	-.005	.967
Amygdala network	Exclusion	.071	.508
	Inclusion	.001	.993
Social pain network	Exclusion	-.029	.791
	Inclusion	-.033	.763

Table S2.

Relationships between Whole-brain Pattern Responses and Other Variables.

a

Variables		Pattern response during exclusion		Pattern response during inclusion	
		r	*p*	r	*p*
Behavioral response to exclusion	Feeling excluded	.016	.883	.182	.092
	Feeling ignored	-.034	.754	-.152	.163
	Feeling hurt	.064	.555	-.053	.624
Relationships with players	Average communication	.155	.149	-.046	.669
	Average closeness	-.156	.148	-.051	.636
Psychological factors	Depression	.171	.111	-.026	.808
	Perceived stress	.077	.477	-.079	.466
	Anxiety	.039	.720	-.038	.727
	Extraversion	.030	.784	.105	.330

b

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**38.095**	**9.385**	**4.059**	**0.001**	**19.433**	**56.758**
Pattern response during exclusion	0.123	2.283	0.539	0.957	-4.417	4.663
Average closeness	-4.343	3.746	-1.159	0.250	-11.793	3.107
Pattern response x Average close	0.884	0.946	0.934	0.353	-0.998	2.765

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**24.196**	**5.135**	**4.712**	**0.000**	**13.985**	**34.408**
Pattern response during exclusion	**3.019**	**1.242**	**2.431**	**0.017**	**0.549**	**5.489**
Average communication	1.214	1.469	0.827	0.411	-1.707	4.136
Pattern response x Average comm	-0.264	0.324	-0.813	0.419	-0.909	0.381

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**36.759**	**3.544**	**10.371**	**0.000**	**29.709**	**43.805**
Pattern response during inclusion	3.241	2.656	1.221	0.226	-2.039	8.521
Average closeness	-0.787	1.420	-0.554	0.581	-3.610	2.037
Pattern response x Average close	-0.669	1.144	-0.584	0.561	-2.944	1.607

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**32.976**	**2.026**	**16.273**	**0.000**	**28.947**	**37.006**
Pattern response during inclusion	**2.987**	**1.477**	**2.010**	**0.048**	**0.031**	**5.904**
Average communication	0.780	0.628	1.243	0.217	-0.468	2.029
Pattern response x Average comm	-0.510	0.475	-1.074	0.286	-1.456	0.435

Note. (a) Correlations between loneliness and other variables, including behavioral responses to social exclusion, contextual factors of the Cyberball, and other psychological factors. (b) Moderation effects of contextual factors of social exclusion (relationships with two players) on the relationship between pattern response and loneliness.

국문 초록

사회적 배제의 신경반응패턴과 노년기 고독감의 관계

사회적 고립은 노년기 정신 건강과 신체 건강에 영향을 미치는 주요요인이다. 그 중 사회적 배제는 다른 사람으로부터 무시되거나 주목 받지 못하는 구체적인 사회적 고립 경험이다. 사회적 존재로서 인간의 뇌는 유익한 사회적 관계를 형성하고 유지하는 기능을 한다. 사회적 배제의 신경기전을 이해하면 사회적 배제 경험과 관련된 심리기제에 대한 통찰을 얻을 수 있다. 또한, 사회적 배제의 신경반응패턴과 고독감의 관계를 확인함으로써, 고독감이 만성적으로 유지되도록 하는 사회인지 특성을 이해할 수 있다. 본 연구는 가상의 공놀이 게임(Cyberball) 과제 중 신경활성화의 다변량 패턴분석을 통해 한국 노인 샘플에서 사회적 배제의 신경반응패턴을 찾았다. 또한, 발견된 사회적 배제의 신경반응패턴이 고독감과 관련된 개인차를 보이는지 확인했다. 88명의 한국 노인을 대상으로 과제 중 신경활성화로 사회적 배제조건과 참여조건을 구분하는 예측모델을 개발했으며, 이 모델은 정확도 0.632, AUC 0.693의 예측력을 보였다. 복셀과 영역의 예측자 중요도를 분석한 결과, 모델의 예측에 가장 많이 기여한 영역은 양측 하두정소엽, 배내측 전전두피질, 설전부, 편도체, 복측선조체였다. 이 영역은 마음을 추론하는 능력과 관련된 mentalizing 네트워크 그리고 편도체를 중심으로 연결된 amygdala 네트워크에 속한다. 또한, 평소 고독감을 높게 지각할수록 사회적 배제 경험 시에 높은 신경반응성을 보였다. 본 연구는 사회적 배제의 신경반응성이 다양한 사회적 기능을 하는 영역에 넓게 분산된 형태의 패턴을 보이며, 고독감을 많이 느끼는 노인은 사회적 배제 상황에 더 민감하게 반응하는 특성이 있음을 확인했다. 한국 노인 샘플에서 사회적으로 배제되는 고립 경험 시에 사용되는 인지적 특성에 대한 이해를 제공하고, 고독감에 대한 개입 시 사회인지 특성에 초점을 두는 개입방법의 중요성을 시사한다.

주요어 : 사회적 배제, 고독감, 다변량 패턴분석(MVPA), 노년기

학번 : 2018-24925

Master's Thesis of Psychology

Neural Pattern Signature of Social Exclusion Predicts Loneliness in Older Adults

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August 2020

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심리학석사 학위논문

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오나은

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지도교수 최 진 영

이 논문을 심리학석사 학위논문으로 제출함
2020년 8월

서울대학교 대학원
심리학과 임상심리학 전공

오 나 은

오나은의 석사 학위논문을 인준함
2020년 8월

위 원 장	최 인 철	(인)
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Abstract

Social isolation is a critical factor that impacts our mental and physical health in late-life. A specific instance of social isolation is the experience of being ignored or unnoticed by others, namely social exclusion. As the brain is the key organ for forming and maintaining salutary connections with others, understanding the brain mechanisms of social exclusion is important for understanding psychological processes that would complement the existing self-report measures. In addition, examining the relationship between the neural signature response of social exclusion and loneliness outcome can provide insight into the social cognitive aspect of loneliness. This study aims to identify a neural pattern signature of social exclusion in older adults, using multivariate pattern analysis of neural activations during a Cyberball task, and to verify loneliness-related individual differences in the signature. A predictive model was developed to distinguish between a social exclusion and inclusion condition, using a widely distributed neural activation pattern of 88 older adults. The fMRI pattern classifier distinguished social exclusion and inclusion with an accuracy of 0.632 and AUC of 0.693. Voxel-level and region-level feature importance analysis demonstrated that areas contributing most to the prediction are the bilateral inferior parietal lobe, dorsomedial prefrontal cortex, precuneus, amygdala, and the ventral striatum. In relation to individual differences in loneliness, those who perceived more loneliness showed higher neural signature responses during social exclusion. These findings demonstrate that the neural signature of social exclusion is characterized by distributed networks of functional regions, especially the mentalizing and amygdala networks, and that older adults who are lonely may be more sensitive to being socially excluded.

Keywords : social exclusion, loneliness, multivariate pattern analysis (MVPA), older adults
Student Number : 2018-24925

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Chapter 1. Introduction

1.1 Social Isolation

Humans are social beings that are greatly affected by social relationships, processes, and behavior. We are intrinsically driven by a desire to form and maintain social connections (Baumeister & Leary, 1995; James, 1890) and social factors can be caring and protective. Thus, social isolation, i.e. being physically or emotionally separated from others, can be a critical threat to mental and physical health. It is known to be related to depression (Cacioppo et al., 2006; VanderWeele et al., 2011), alcohol abuse (Åkerlind & Hörnquist, 1992), suicidal ideation (Rudatsikira et al., 2007), social anxiety (Kearns et al., 2014), and impulsivity (Savci et al., 2015). It is also a risk factor of cognitive decline and dementia (Kim, 2015; Wilson et al., 2007), cardiovascular health (Cacioppo et al, 2002; Valtorta et al., 2016), reduced immune function (Kiecolt-Glaser et al., 1984, Cacioppo et al., 2015), and the increased likelihood of mortality (Holt-Lunstad & Smith, 2018).

The impact of social isolation is especially consequential in late-life. Loneliness, a perceived feeling of isolation, is generally retained at a constant level until the age of 65 but rapidly increases in the old-old population (Mund et al., 2019). It is prevalent in older populations accounting to 30% of elders reporting the feeling of loneliness (Yang & Victor, 2008).

1.2 Social Exclusion

Social exclusion is a pointed, specific instance of social isolation. It is the experience of being ignored or unnoticed by others. We experience being socially

excluded from others in everyday life, such as being uninvited to a social outing, one's requests being ignored, or being bullied in a social group. Many of these threats to social connections are subtle, ambiguous, and sometimes unintentional (Banki, 2012; Kerr & Levine, 2008; Richman & Leary, 2009). This is a distinct type of social isolation that is different from other types of social isolation experiences, such as being explicitly rejected via cues that one is not wanted in a social relationship (Williams, 2007). Social exclusion results in negative psychological outcomes such as feeling ignored, excluded, hurt, sad, or angry, and can lead to depression and alienation in the long run. The experience of social exclusion, or ostracism, can be measured through experimentally administered social situations, in which participants are led to believe they are being ignored or unnoticed by others. One well-known task that induces ostracism is the Cyberball paradigm where participants experience exclusion when they stop receiving the ball from other players during a virtual ball-tossing game (Hartgerlink et al., 2015).

1.3 Neural Mechanism of Social Exclusion and Loneliness Outcome

In the social neuroscience perspective, the brain is the key organ for forming, monitoring, maintaining, repairing, and replacing salutary connections with others (Cacioppo & Berntson, 1992). Understanding the how the brain processes and reacts to information during social exclusion can provide an additional window into psychological processes that complement self-report measures or biological measures (Berkman & Falk, 2013). It is especially useful in situations where the underlying psychological processes are difficult to capture when utilizing other methods, such as populations that find it challenging to express vague emotions with words. Using the brain as a predictor of the psychological state (e.g. social exclusion)

is a modeling approach that is consistent with this perspective. This 'decoding' model extracts latent, psychological factors as functions of brain data via transformation of high-dimensional brain data into a potentially low-dimensional representation in which they exhibit certain desired characteristics, e.g. good classification (Haufe et al., 2014).

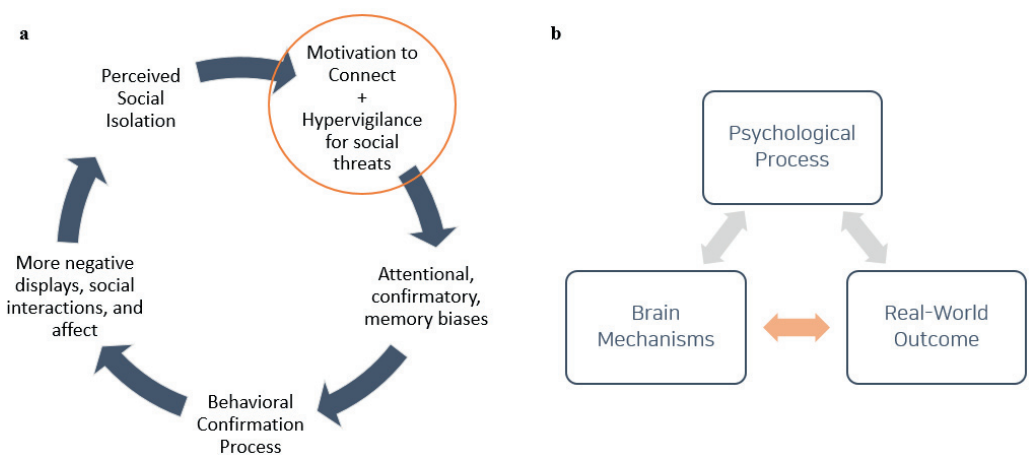
Moreover, examining the relationship between the neural signature response of social exclusion and loneliness outcome can provide insight into the social cognitive aspect of loneliness. Loneliness is defined as perceived social isolation and occurs when we have a mismatch between the social relationships that we have and those we want (Perlman & Peplau, 1981). According to the social cognition framework of loneliness (Figure 1a), lonely individuals have maladaptive social cognition processes that maintain or even aggravate the feeling of loneliness (Cacioppo & Hawkley, 2009). The brains of lonely individuals are on high alert for social threats compared to the non-lonely, so lonely individuals tend to view their social world as threatening and punitive. Specifically, loneliness can trigger implicit hypervigilance for social threats, which in turn produces attentional, confirmatory, and memory biases that may induce more loneliness. This theoretical model emphasizes the social cognitive aspect of loneliness and is supported by some pieces of evidence from behavioral and neuroimaging research (Cacioppo et al., 2009; Cacioppo & Hawkley, 2005). Masi et al. (2011) also found that the greatest effect on loneliness was seen with interventions that addressed maladaptive social cognition, e.g. interventions regarding automatic negative thoughts as faulty hypothesis that need to be verified.

Few studies have attested the effect of loneliness on the perception of social threat yielded from 'social exclusion.' Vanhalst et al. (2015) showed that chronically lonely adolescents were hypersensitive to social exclusion and hyposensitive to social

inclusion. Wesselmann et al. (2012) collected real-time affective response during Cyberball and showed that lonely individuals had slower affective decrease when ostracized but quicker affective increase when included. These inconsistent results on response to social exclusion in lonely individuals emphasize the need to reexamine the relationship between neural reactivity to social exclusion and loneliness.

When lonely individuals experience social exclusion, the cognitions of implicit hypervigilance and negatively biased interpretation of the social world may arise, and these psychological processes may be represented as increased neural reactivity to the exclusion situation. Thus, as illustrated in Figure 1b, identifying the psychological processes during social exclusion, represented by neural reactivity, and their relation to loneliness outcome improves the ecological validity of the neural mechanism model of social exclusion by connecting neural measures to outcomes beyond the lab (Berkman & Falk, 2013).

Figure 1.
Theoretical Background of the Research on Neural Mechanisms of Social Exclusion and Loneliness Outcome



Note. Figure 1a is modified from Cacioppo & Hawkley (2009) and Figure 1b is modified from Berkman & Falk (2013).

1.4 Multivariate pattern analysis of Neural mechanisms

Social and emotional states are neurally represented in distributed patterns across a number of brain regions. Neuronal representations of emotion categories were found to be distributed across a number of cortical and subcortical brain regions based on recent functional neuroimaging studies (Kragel et al., 2015; Saarimaki et al., 2016).

Human and animal research on the effects of social isolation on the brain suggests the involvement of multiple, functionally distinct brain mechanism, including social threat surveillance and aversion (amygdala, anterior insula, anterior cingulate), social reward (ventral striatum), and attention to one's self-preservation in a social context (orbitofrontal cortex, medial prefrontal cortex, superior temporal sulcus, temporal parietal junction) (Cacioppo et al., 2015). Since social exclusion is a subtle, yet complex experience, it can be assumed that various brain mechanisms will be involved in processing and responding to the exclusion situation.

In this study, we implemented multivariate pattern analysis (MVPA) to understand the neural mechanism of social exclusion. Previous studies on social isolation, specifically social exclusion and loneliness, have employed mass-univariate analysis of brain data. This method provides a single summary statistic of the most significantly activated voxel in a brain region (Kragel et al., 2016). It is limited in that it cannot capture the subtle intensity variations within a significant region, lacking sensitivity to subtle spatial patterns in the brain. Also, these models are focused on how well they fit to a particular sample of data and do not examine out-of-sample generalizability of models.

MVPA is an analysis approach that assesses information contained in patterns of brain activity, such as by learning a mapping from multiple voxels to a categorical or continuous variable. MVPA aims to find mental state-specific patterns that emerge

across locally distributed populations of neurons within a region or across neural networks at larger spatial scales (Kragel et al., 2016). These models have higher sensitivity to distributed neural correlates of the underlying representation. Moreover, it takes on error analyses and measures of signal detection theory to check models for generalizability to various samples (Woo & Wager, 2015; Yarkoni et al., 2017). Thus, it may be more appropriate to utilize MVPA in understanding the widely distributed neural mechanisms underlying social exclusion.

1.5 Research Purpose and Hypotheses

This paper aims to identify the neural signature of social exclusion, specifically in older adults, and to examine the individual differences of the signature in relation to self-reported loneliness. First, we will train a model that predicts the social exclusion versus inclusion state from brain activations during exclusion and inclusion condition of Cyberball. In other words, we hypothesize that a MVPA model will identify the neural pattern which distinguishes the brain's exclusion and inclusion state. Second, it is hypothesized that the neural patterns of social exclusion will be widely distributed in the predefined networks, namely the mentalizing network, amygdala network, and social pain network. Lastly, it is hypothesized that the neural pattern response to social exclusion will be associated with individual differences in loneliness.

Chapter 2. Methods

2.1 Participants

Eighty-eight healthy older adults (51 females, Mean age=70.95, S.D. of age=6.46) from the Korean Social Life, Health, and Aging Project (KSHAP) participated in the study. These participants lived in the same neighborhood in a rural area in South Korea. Of the initial 110 participants of the 4th wave of KSHAP, we excluded those with a history of psychiatric or neurological diseases, traumatic brain injury, loss of consciousness following the injury, or mild cognitive impairment, in order to sample normal aging adults. Those who did not comprehend the social exclusion task, showed excessive head motion during the fMRI scan, had vision problems, or were not right handed were additionally excluded.

To control for baseline physiological states of participants, they were instructed to sleep well, be rested, and not exercise, drink or eat anything before the scan. All participants provided written information consent after experimental procedures were described and received an honorarium for their participation. The study was approved by the Seoul National University Institutional Review Board.

Table 1.

Descriptive Statistics of Participant Information

Variable	*n*	%	*M*	*SD*
Gender				
Female	51	58		
Male	37	42		
Age	88	100	70.95	6.46
Years of education	88	100	7.45	6.46
0 – 5y	15	20.50		
6y	42	39.80		
7 – 12y	38	32.90		
12y or more	10	6.70		
Number of chronic diseases [a]	88	100	1.37	1.05
Self-rated health status	88	100	2.98	0.83
Loneliness	88	100	36.50	9.32
Depression	88	100	9.35	6.49
Perceived stress	88	100	12.78	9.67
Anxiety	88	100	1.22	1.62
Extraversion	88	100	25	5.33
Response to exclusion				
Recognized exclusion [b]	88	100	1	0.00
Feeling excluded	88	100	4.80	0.70
Feeling ignored	88	100	1.98	1.50
Feeling hurt (sad)	88	100	1.88	1.50
Average communication with players	88	100	2.76	1.07
Average closeness with players	88	100	1.35	0.94

[a] Chronic diseases included hypertension, diabetes, hyperlipidemia, osteoporosis, cancer, myocardial infarction, angina pectoris, cataract, and glaucoma.

2.2 Social Exclusion Task : Cyberball

In order to induce a situation where participants experience social exclusion, we adapted a modified version of the Cyberball task. In the original task, participants played a virtual-ball tossing game with unknown players online and at some point during the game stopped receiving the ball from other players, perceiving themselves to be excluded (Williams et al., 2000). This experience of social exclusion is known to cause increased negative emotions and higher vulnerability to belonging, control, self-esteem, and meaningful existence (Williams, 2009).

In this study, participants were led to believe that they were playing the Cyberball with participants that came to the MRI center together from their village. Before the task, the three participants that came to the center together were asked what kind of

relationship they have and how long they have known each other (in years). They were also individually asked how frequently they communicate with the others (1=none, 5=everyday) and the extent to which they feel close to the others using the five-point Likert scales (1=don't know, 5=very close). Although the participants lived in the same neighborhood, they had different levels of acquaintance to one another from strangers to close friends or spouse. During the task, participants were instructed to press left or right buttons on a fMRI-compatible response box in order to throw the ball to a player on the left or right.

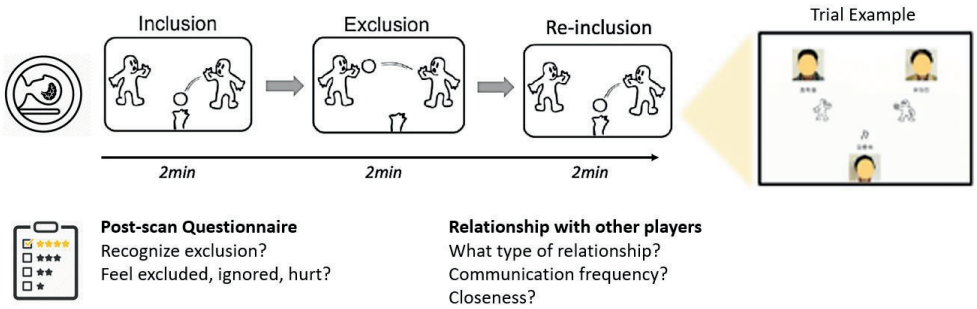
As many of the participants were older adults living in rural areas with fewer years of education, we expected some of them to have difficulties in fully understanding and mentally visualizing the virtual ball-tossing environment. Thus, before the task, participants played a short, face-to-face ball-tossing game with an actual plastic ball and a practice session playing the Cyberball with computers. During the task, participants were expressed as animated characters and given names and faces of the three players next to each character. The participant's character was positioned in the bottom center and the other two players were positioned on the upper left and right in random order (Figure 2).

In reality, participants were tested individually and the throws of other players were controlled by a computer program. The task comprised of three blocks of social interaction. In the inclusion condition, participants were given the ball often throughout the game for 50% of all throws. In the exclusion condition, after a few included throws (i.e. 5 throws), participants were not given the ball at all, thus experiencing social exclusion. In the re-inclusion condition, after a few included throws (i.e. 5 throws), participants were given 100% of throws. Each condition lasted approximately 2 minutes (i.e., total of 6 minutes of 130 throws on average). Brief

random delays of 0.5s-3.5s were inserted before each player made a throw to enhance participants' belief that they were playing with other people.

Figure 2.

Cyberball Paradigm



2.3 Post-scan questionnaires and Loneliness survey

Following the MRI scan, participants rated how they felt about each state of the task (Zadro et al., 2003). They were asked if they recognized that they received less or more tosses in different conditions (yes or no), in order to check if manipulation of ostracism was successful. They also rated on various reactions to the exclusion condition: how much they felt they were excluded, ignored, and hurt (or sad) using five-point Likert scales (1=not at all, 5=very much). As this experiment used deception to induce social exclusion experience, debriefing procedures were administered after the experiment.

Loneliness was measured with the Korean version of the 20-item UCLA-r Loneliness scale (Kim, 1997; Russell, 1980). This scale measured overall perceived loneliness and satisfaction of social relationships. It consisted of 20 items in four-point Likert scales that measure various social and affective aspects of loneliness, without explicitly asking if one 'feels lonely' (e.g. 'I lack companionship,' 'There are people I feel close to,' 'I feel isolated from others,' 'People are around me but

not with me').

We administered additional questionnaires in order to take other factors into account, including the Geriatric Depression Scale (Korean Version) (GDS; Brink et al., 1982; Jung et al., 1997), Geriatric Anxiety Inventory – Short Form (Korean Version) (GAI-SF; Byrne & Pachana et al., 2007), Perceived Stress Scale (Korean Version) (PSS; Baek, 2010; Cohen, Kamarck, and Mermelstein, 1983), Big Five Inventory (Korean Version) (BFI-K; Kim et al., 2010; John, Donahue, & Kentle, 1991), and a health survey about the number of chronic diseases they have and a self-reported health status (1=bad, 5=very good). Chronic diseases included hypertension, diabetes, hyperlipidemia, osteoporosis, cancer, myocardial infarction, angina pectoris, cataract, and glaucoma.

2.4 FMRI acquisition and preprocessing

All MRI data were acquired on a 3T SIEMENS MAGNETOM Trio TIM Syngo MR with 32 channel coil and GRAPPA. Whole-brain fMRI data of 180 volumes were acquired during Cyberball, using echo-planar imaging(EPI) sequence with the following parameters: repetition time (TR)=2000ms, echo time (TE)=30ms, flip angle (FA)=79°, field of view (FOV)=240mm, 30 slices (3x3x4mm^3 voxels) parallel to the anterior commissure-posterior commissure line. Structural data were acquired using a T1-weighted MP-RAGE with the following parameters: TR=23000ms, TE=2.36ms, FA=9°, FOV=256mm, 1x1x1mm^3 voxels. Stimulus presentation and behavioral data acquisition were administered using PsychoPy (Peirce et al., 2019).

Functional images were corrected for differences in slice acquisition timing to the first slice and were motion corrected using SPM12. They were warped to SPM's

normative atlas (East Asian MNI152) using warping parameters estimated from co-registered structural images and interpolated to 2x2x2mm^3 voxels. Images were smoothed with a $6mm$ FWHM Gaussian kernel in order to ameliorate intersubject differences in localization while retaining sensitivity to fine-scale activity patterns. Subjects with excessive head motion (absolute motion > 3, mean motion > 0.5, max motion > 4.5, mean frame-to-frame displacement > 0.15) were excluded from the analysis, resulting in 88 subjects.

Voxel-wise statistical parametric maps for each task condition were estimated using the first-level GLM analysis. For each individual, three task conditions were constructed for regressors of interest, corresponding to 2-min inclusion, exclusion, and reinclusion periods. For each task regressor, a Boxcar function was convolved with SPM12's canonical hemodynamic response function. Also, a set of nuisance covariates were included to capture noise (a constant term for the run and six mean-centered motion parameter estimates) and fixation-cross epoch was not included as a regressor since the model may become over-parameterized. A high-pass filer of 128s was applied to remove low-frequencies from the data. The voxel-wise statistical parametric maps for exclusion and inclusion conditions that were calculated for each subject were used as features in multivariate pattern analysis (MVPA).

To compare with MVPA results, we analyzed traditional encoding models with general linear modeling (GLM) for exclusion and inclusion contrasts, as well as [exclusion > inclusion] and [inclusion > exclusion] contrasts using a predefined mask of social cognition and behavior (Figure 3).

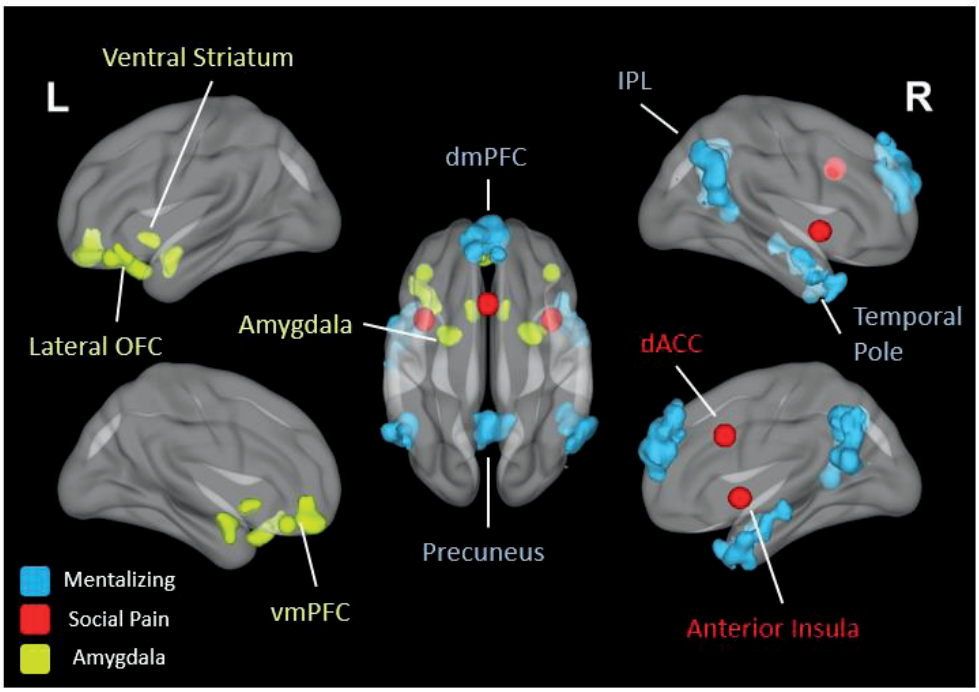
2.5 Multivariate Voxel Pattern Analysis

We used a linear support vector machine (SVM) to train a multivariate pattern classifier that predicts exclusion or inclusion conditions from brain activations. Linear classifiers are advantageous as they are simple with comparable estimation accuracy (Misaki et al., 2010) and are appropriate for analyzing brain data as they combine information from different measurement channels in a weighted sum, which resembles the working principle of neurons (Kriegeskorte, 2011).

First, we selected features with *a priori* maps of functional networks related to social cognition and behavior, which may be closely involved in social isolation based on previous literature (Figure 3). The mentalizing network, including the dorsomedial prefrontal cortex, inferior parietal lobe, temporal pole, and precuneus, was defined from voxels associated with 'mentalizing' term based on meta-analytic database Neurosynth (Yarkoni et al., 2011; https://neurosynth.org/). The amygdala network included the amygdala defined from AAL2, ventral striatum from Harvard-Oxford atlas, lateral orbitofrontal cortex from coordinates used in Bickart et al. (2012), and ventromedial prefrontal cortex from Neurosynth. The social pain network consisted of the dorsal anterior cingulate and bilateral anterior insula extracted from 8-mm-radius spheres around coordinates of peak voxels in "social* & pain*" Neurosynth maps used in Schmälzle et al. (2017). The three networks included 4594 voxels, 1636 voxels, and 343 voxels each and, thus comprised a total of 6573 voxels.

Figure 3.

A Priori Maps of Three Functional Networks related to Social Cognition and Behavior



Note. Feature selection with a priori maps of three functional networks related to social cognition and behavior: mentalizing network, amygdala network, social pain network. Lateral OFC (lateral orbitofrontal cortex, vmPFC (ventromedial prefrontal cortex), dmPFC (dorsomedial prefrontal cortex), IPL (inferior parietal lobe), dACC (dorsal anterior cingulate)

Then, SVM classifier with a linear kernel, L2-regularization parameter C=1.0, and hinge loss function was implemented using scikit-learn (based on libsvm). SVM is a supervised learning, binary classifier that finds a hyperplane that separates two different classes of data points by the largest distance. The algorithm depends on the data only through dot products ($h(x) = g(\omega^T x + b)$, where g is the sign determining class) and finds the hyperplane with maximum margin while minimizing margin errors (soft-margin). SVM is widely used in bioinformatics and other disciplines due to its high accuracy, ability to deal with high-dimensional data, and flexibility in modeling diverse sources of data (Schölkopf et al., 2004).

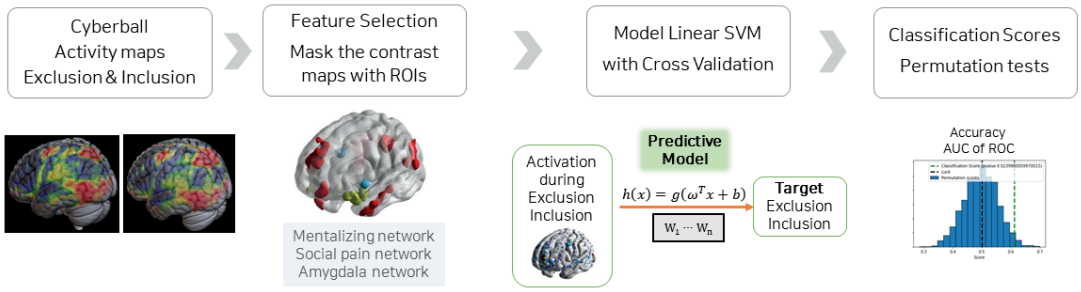
The pattern classifier was trained on first-level contrast images for exclusion and

inclusion conditions. Leave-one-subject-out cross-validation was implemented where training was performed with n-1 subjects and testing was then applied to one remaining subject, and repeated across all subjects. This procedure allows the model to estimate whether the neural signatures of social exclusion are consistent across individuals. Voxel activation values were normalized during cross validation to ensure independence between training and test datasets. The classification score was defined as the accuracy score and the area under the Receiver Operating Characteristic (ROC) curve (AUC) which was averaged across cross-validation folds.

To test whether classification scores exceeded chance level, a chance-level performance percentage was derived as a ratio of 1 over the number of categories, thus 50% in this study. Also, permutation tests were conducted to simulate the probability distribution of the classification and thus provided confidence limits of the chance-level accuracies. Each permutation step included shuffling of condition labels and rerunning the classification with cross-validation, repeated 5000 times. After testing classification scores of the model, further interpretation and analysis were administered on a model that was trained on the full sample. Figure 4 illustrates the overall procedure of MVPA used in this study.

Figure 4.

Multivariate Pattern Analysis Procedure



Note. Multivariate pattern analysis was conducted with the following steps. 1) First-level contrast maps of exclusion and inclusion conditions were estimated for each subject, 2) Voxels within an a priori mask of three functional networks related to social cognition and behavior were selected, 3) Linear SVM was trained with leave-one-subject-out cross-validation using the masked contrast maps of exclusion and inclusion, 4) Permutation tests were used to validate the classification score of the model.

2.6 Feature Importance Analysis

Once the model predicting social exclusion condition has been trained, it is important to interpret the model, i.e. identify which voxel or region features are most predictive of the outcome. The desired goals of brain decoding models are to first predict the state with neural responses and then to determine specific regions that contain relatively more information about the predicted state.

Unlike encoding models whose parameters indicate how external variables are encoded in the brain data, parameters (weights) of decoding models cannot be directly interpreted because those weights depend not only on brain activity of interest but also on noise components in the data (Haufe et al., 2014). Thus, feature importance can be an alternative method for parameter interpretation when employing multivariate pattern analysis to understand neural mechanisms of psychological states.

One common, reasonably efficient, and reliable technique is permutation feature

importance. Permutation feature importance is the percent increase in prediction error (1-AUC) after a feature's value is permuted, which breaks the relationship between the feature and the true outcome (Altmann et al., 2010; Breiman 2001; Fisher et al., 2018) Another feature importance technique is the drop-column, or "lesioned", feature importance. It is the percent increase in prediction error after a feature is removed from the model (Whelan et al., 2014). For both importance metrics, higher values indicate that the feature has higher relative importance to the prediction and values of 0 or less indicate that the feature is not important to the prediction.

We calculated permutation feature importance and lesioned feature importance at the voxel-level, region-level, and network-level. Voxels were grouped together as regions and networks to calculate feature importance at the region-level and network-level.

2.7 Quantifying the Neural Signature Response to Social Exclusion

In order to examine the loneliness-related individual differences in neural sensitivity to social exclusion, the level of pattern response was calculated by taking the dot product of the pattern weights ($\vec{w}$) and vectorized activation contrast maps for each condition ($\vec{x}$), i.e. ($\vec{w} \cdot x$). This yields a scalar value that is the weighted average of activation for each subject in each condition, representing the expression of the pattern in response to exclusion or inclusion state (Wager et al., 2013; Lada et al., 2020).

We examined the level of pattern response during exclusion and inclusion of each subject and its association with individual differences in loneliness. Pearson's correlation analysis was conducted to examine the trend of associations between

pattern responses and loneliness. Then, multiple regression analyses predicting loneliness with pattern responses were administered, controlling for basic demographic factors (gender, age, education, health status) and task-related contextual factors (average communication frequency and closeness with two other players). Finally, we tested whether the relationships between loneliness and pattern responses during exclusion versus inclusion were significantly different. We first compared the correlation coefficients *r* of loneliness and pattern responses during exclusion versus inclusion, via one-tailed Steiger's Z test (Meng et al., 1992). Then, using the Potthoff analysis (Potthoff, 1966), we created a dummy variable to code the exclusion/inclusion conditions and included the interaction between the dummy variable and pattern responses as a predictor in a multiple regression predicting loneliness. The significance of the interaction term would indicate that the regression coefficients of pattern responses during exclusion and inclusion were significantly different.

In addition, network-level pattern response can be calculated by taking the dot product of pattern weights of a particular network and its corresponding voxel activations. We calculated separate pattern responses for the three functional networks, mentalizing network, amygdala network, and social pain network, and examined their correlations with loneliness. If the network-level patterns of social exclusion show individual associations with loneliness, it may be suggested that certain networks are relatively more related to loneliness and, thus, the neural patterns of social exclusion are organized in a modular rather than an integrated fashion. It may also indicate that certain brain functions are employed more than other functions when experiencing social exclusion in lonely adults.

To examine whether pattern responses were related to factors other than loneliness,

correlation analyses were conducted with behavioral responses to exclusion, contextual factors related to the Cyberball, and other psychological variables. In order to show that the relationship with other players of the Cyberball was not the driving factor of neural responses to social exclusion, we tested whether it had moderation effects on the relationship between pattern response and loneliness.

Chapter 3. Results

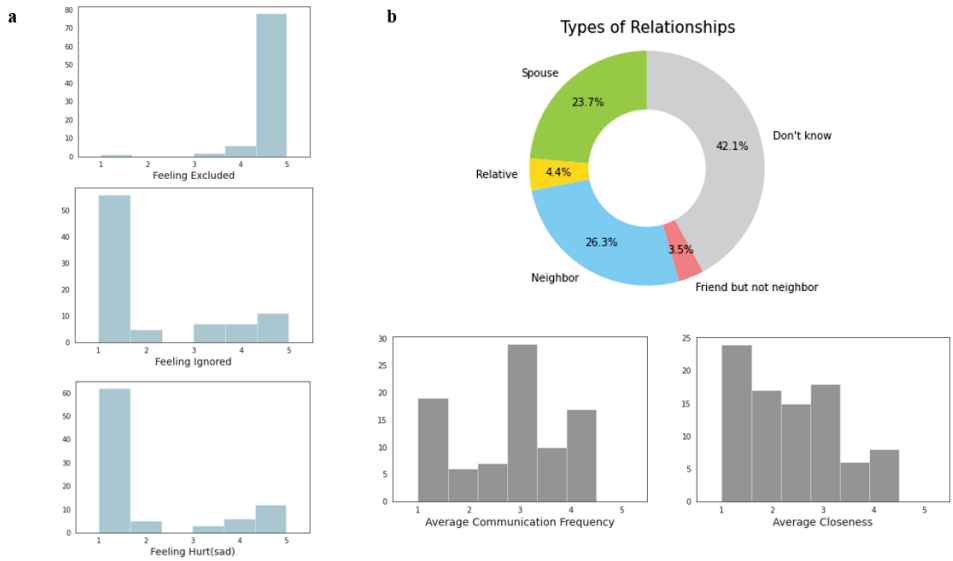
3.1 Behavioral results

Behavioral results confirmed that all participants recognized that they received less ball tosses during the exclusion condition of the Cyberball, indicating successful manipulation of ostracism. (Figure 5a) Most participants felt excluded from other players during the exclusion condition (96.6% reported over 4), whereas only a subset of them felt ignored (70.9% reported 2 or less) or hurt(sad) (76.2% reported 2 or less).

As shown in Figure 5b, of all the relationships that participants had with other players, 42.1% of participants did not know each other, 29.9% were neighbors or friends, and 28.1% were spouses or relatives. Additional information on the duration of relationship, communication frequency, and closeness with other players can be found in Supplementary Figure S1. The average frequency of communication and the average feeling of closeness with the two other players represents the contextual factors that contribute to the specific instance of social exclusion. Indeed, variances in social relationships of people we interact with may effect one's response to being socially excluded from them and one's overall feeling of loneliness (Wirth & Williams, 2009). As this study mainly focuses on the general situation of social exclusion and its association with loneliness, the relationships with other players of the task were controlled for in later analysis. Nevertheless, we provided preliminary analysis of the effects of contextual factors on neural sensitivity to social exclusion and loneliness.

Figure 5.

Task-related Variables



Note. (a) Behavioral responses to the social exclusion task. (b) Relationships with two other players of the task.

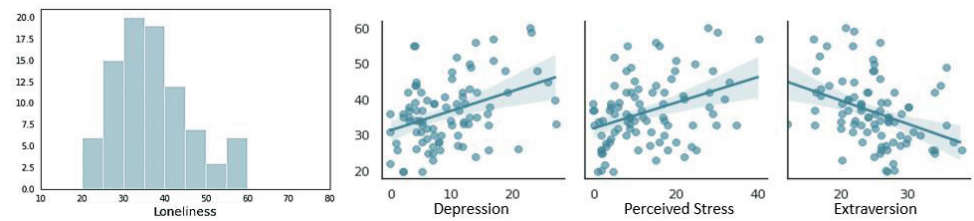
As shown in Table 1 and Figure 6, participants reported different levels of loneliness in life (Mean=36.5, S.D.=9.32). Loneliness was positively correlated with other psychological states/traits such as depression (r=.383, p<.01) and perceived stress (r=.373, p<.01), negatively correlated with extraversion personality (r=-.372, p<.01), but was not related to age, education or physical health. In line with previous findings, loneliness can be considered a psychological state that consists of social and emotional aspects that are related to but distinct from other states or traits such as depression, anxiety, and perceived stress (Cacioppo et al., 2000; Cacioppo et al., 2010; Domènech-Abella, 2019). In addition, loneliness was positively correlated with feeling hurt in response to the social exclusion task (r=.239, p<.05) and was not related to average frequency of communication or the average feeling of closeness with other players of the task. Considering that lonely individuals reported stronger behavioral responses to social exclusion, we can anticipate individual differences

related to loneliness in the neural sensitivity to social exclusion, which seem to be independent from situational factors such as relationships with other players of the task.

Figure 6.

Loneliness and its Relation to Other Variables

a



b

	Age	*Self-reported Health*	*Num of Chronic diseases*	*Depression*	*Perceived stress*	*Extraversion Personality*	*Feeling Hurt*	*Average Communication with players*	*Average Closeness with players*
Corr	-.006	-.163	-.207	.383**	.373**	-.372**	.239*†	-.110	-.144
p	.954	.128	.053	.000	.000	.000	.025	.309	.181

*p<.05, **p<.01, †Spearman's correlation

Note. (a) Histogram of loneliness and scatterplot of its relation with other variables. (b) Correlation between loneliness and other variables, including age, health status (self-reported heath, number of chronic diseases), depression, perceived stress, extraversion personality, and task-related variables (feeling hurt response, average communication and closeness with other players).

3.2 FMRI Pattern Signature

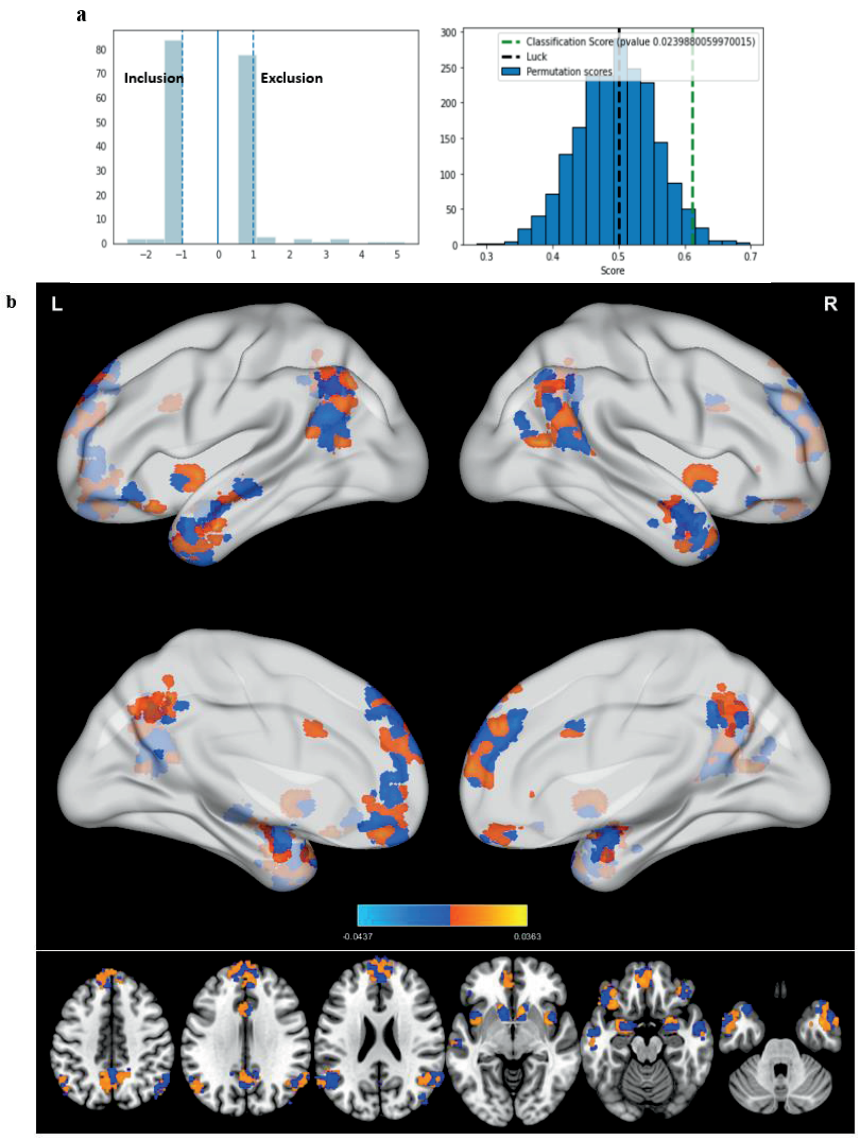
The linear SVM classifier discriminated social exclusion and inclusion with an accuracy of 0.632 (95% CI: [0.576, 0.685]) and AUC of ROC curve of 0.693 (95% CI: [0.595, 0.791]). The classification scores were significantly above chance level (chance level 0.5, permutation significance $p < .05$) (Figure 7a).

The regions with the highest peak voxel weights included the bilateral IPL, temporal pole (positive weights), amygdala, and ventral striatum (negative weights), belonging to the mentalizing network and the amygdala network. Within each region, some regions had more positive weights (bilateral anterior insula, dACC, precuneus,

vmPFC) and some had more negative weights (left ventral striatum, left lateral OFC, right temporal pole, left IPL). Other regions, including the bilateral amygdala, right lateral OFC, right ventral striatum, dmPFC, right IPL, and left temporal pole, consisted of similar numbers of positive and negative weights, indicating locally distributed patterns of weights within those regions (Figure 7b).

Figure 7.

Linear SVM Classification Results



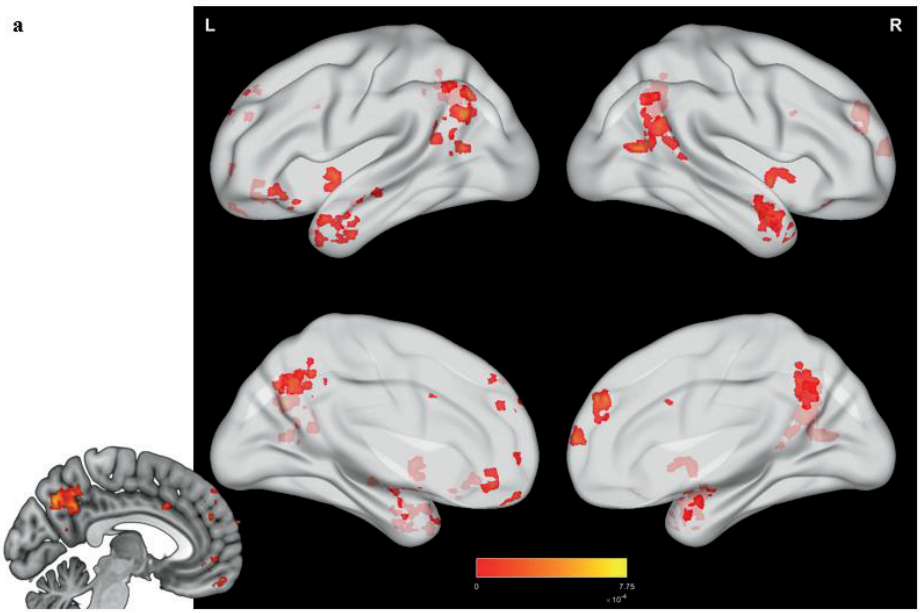
Note. (a) Histogram of projections training separation from the decision boundary and histogram of permutation scores. (b) Pattern weight map, unthresholded for visualization

In order to identify features that were most important to the prediction, we calculated voxel-level, region-level, and network-level feature importance via permutation and "lesioning." Voxel-level permutation feature importance showed that 1704 out of 6573 voxels (26%) had positive importance values and thus contributed to the prediction (Figure 8a). The regions with voxels of the highest importance were the precuneus, dmPFC, right temporal pole, bilateral IPL, left amygdala, vmPFC, right ventral striatum, and left anterior insula. According to region-level feature importance analysis (Figure 8b), the most important regions of the prediction that were commonly ranked highest for both measures of feature importance were dmPFC, left ventral striatum, right temporal pole, right IPL, precuneus, and the left amygdala. These regions are part of the mentalizing network (dmPFC, right temporal pole, right IPL, precuneus), amygdala network (left ventral striatum, left amygdala), and social pain network (right anterior insula). These results were consistent with network-level feature importance analysis with the mentalizing network ranking highest importance followed by the amygdala network and then the social pain network. Although importance scores were correlated with the number of voxels (Spearman's correlation for permutation importance $r=.717$, $p=.002$, lesioned importance $r=-.150$, $p>.100$), the regions that were commonly ranked important by the two measures included very small-sized regions, e.g. the left ventral striatum (107 voxels) and left amygdala (220 voxels).

Figure 8.

Permutation and Lesioned Feature Importance Analysis

a



b

Regions	Permutation Feature Importance	No. of Voxels
dmPFC	0.119	1327
Right Temporal Pole	0.057	431
Right IPL	0.051	902
Precuneus	0.040	663
Left IPL	0.028	681
Left Temporal Pole	0.023	590
Left Ventral Striatum	0.023	107
Left Lateral OFC	0.012	432
vmPFC	0.011	422
Right Anterior Insula	0.011	110
Left Amygdala	0.006	220
dACC	0.006	123
Left Anterior Insula	0.006	110
Right Lateral OFC	0	123
Right Amygdala	0	248
Right Ventral Striatum	0	84

Regions	Lesioned Feature Importance	No. of Voxels
dmPFC	0.113	1327
Left Amygdala	0.034	220
Right Lateral OFC	0.023	123
Left Ventral Striatum	0.023	107
Right Anterior Insula	0.023	110
Right Ventral Striatum	0.011	84
Right IPL	0.011	902
Precuneus	0.011	663
Right Temporal Pole	0.011	431
Right Amygdala	0	248
Left Anterior Insula	-0.012	110
vmPFC	-0.023	422
Left Temporal Pole	-0.023	590
Left IPL	-0.034	681
dACC	-0.034	123
Left Lateral OFC	-0.057	432

Networks	Permutation Feature Importance	No. of Voxels
Mentalizing network	0.414773	4594
Amygdala network	0.221591	1636
Social pain network	0.073864	343

Networks	Lesioned Feature Importance	No. of Voxels
Mentalizing network	0.125	4594
Amygdala network	0.045	1636
Social pain network	0.023	343

Note. (a) Map of voxel-level permutation feature importance. (b) Region-level and network-level feature importance values (permutation and lesioned importance) in descending order and the number of voxels within each region.

In comparison, GLM results showed some commonly overlapping regions involved in exclusion and inclusion conditions, as well as some regions that involved differently in the two conditions. The bilateral middle temporal gyrus (inferior parietal lobe, IPL) and precuneus were activated in both exclusion and inclusion conditions. The bilateral anterior insula and lateral orbitofrontal cortex (OFC) were additionally activated in the inclusion condition. The [inclusion>exclusion] contrast map showed that dorsomedial prefrontal cortex (dmPFC), temporal pole, ventromedial prefrontal cortex (vmPFC), precuneus, IPL, ventral striatum, and lateral OFC were highly activated during inclusion than exclusion. In the [exclusion>inclusion] contrast which was analyzed at the whole-brain level, regions around the 4th ventricle and bilateral inferior occipital gyrus were activated more during exclusion than inclusion (Supplementary Figure S2).

3.3 Neural Signature Response to Social Exclusion and its relationship with Loneliness

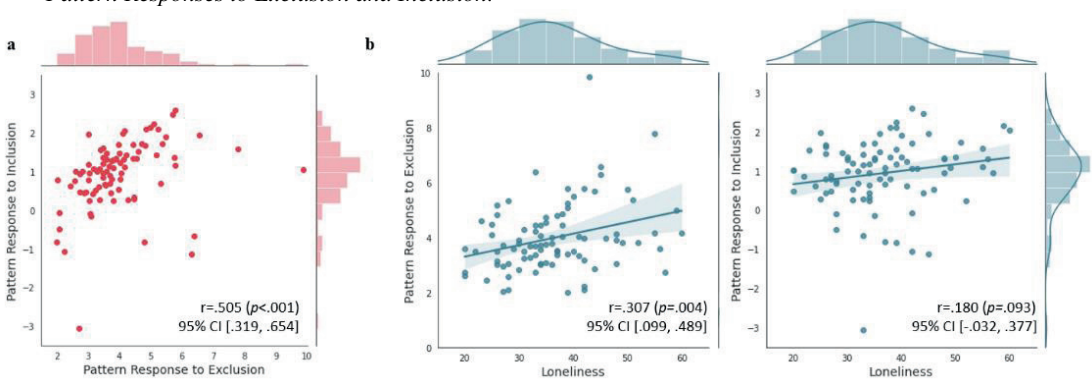
Pattern responses during exclusion and inclusion were calculated for each subject. Individuals with higher pattern response in the exclusion condition showed higher response in the inclusion condition (Spearman's correlation $r=.505$, $p<.001$) (Figure 9a). As in Figure 9b and 9c, whole-brain pattern response during the exclusion condition was positively correlated with loneliness (Pearson's correlation $r=.307$, $p=.004$). Multiple regression predicting loneliness with pattern response during exclusion showed that the model significantly explained 15.4% of the variance ($R^2=.154$, $F(6,81)=2.45$, $p=.031$) and the pattern response during exclusion contributed significantly to the prediction of loneliness (Beta=2.073, $t=2.719$, $p=.008$), after controlling for gender, age, education, health status, and average

closeness or communication with other players. The level of pattern response during the inclusion condition was not significantly correlated with loneliness (Pearson's correlation r=.180, p=.093). In terms of coefficients, the correlation with loneliness was not significantly greater for pattern response during exclusion than for pattern response during inclusion (z=1.223, p=.111). Multiple regression predicting loneliness with pattern expression during inclusion showed that the model did not significantly explain the variance (R^2=.100, F(6,81)=1.492, p=.191) and the pattern expression during inclusion did not predict loneliness (Beta=1.633, t=1.444, p=.153), after controlling for the same variables. As in Figure 9d, although the regression model with the interaction term 'pattern response x conditions' significantly explained loneliness (R^2=.0632, F(3,172)=3.866, p=.01), the regression coefficients of pattern responses during exclusion and inclusion were not significantly different (Beta=.168, t=.249, p=.804).

Of the 88 subjects, there were two outliers of pattern response to exclusion and inclusion. We found similar results when administering the identical analyses after removing the outliers: pattern response to exclusion showed positive correlations with loneliness (r=.311, p=.003) and pattern response to inclusion did not have significant correlations with loneliness (r=.184, p=.088).

Figure9.

Pattern Responses to Exclusion and Inclusion.



c

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**36.789**	**11.812**	**3.114**	**0.003**	**13.286**	**60.292**
Gender	0.368	2.118	0.174	0.863	-3.846	4.581
Age	-0.028	0.152	-0.181	0.856	-0.331	0.275
Education	-0.080	0.244	-0.329	0.743	-0.565	0.405
No. of chronic diseases	**-1.935**	**0.926**	**-2.089**	**0.040**	**-3.777**	**-0.092**
Average closeness	-1.373	1.050	-1.308	0.195	-3.463	0.717
Pattern response during exclusion	**2.073**	**0.762**	**2.719**	**0.008**	**0.556**	**3.590**

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**42.647**	**11.910**	**3.581**	**0.001**	**18.950**	**66.343**
Gender	0.642	2.181	0.294	0.769	-3.697	4.981
Age	-0.001	0.157	-0.008	0.993	-0.313	0.311
Education	-0.119	0.252	-0.471	0.639	-0.620	0.383
No. of chronic diseases	-1.897	0.958	-1.980	0.051	-3.804	0.010
Average closeness	-1.746	1.071	-1.631	0.107	-3.877	0.385
Pattern response during inclusion	1.634	1.131	1.444	0.153	-0.617	3.884

d

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**31.125**	**1.750**	**17.787**	**0.000**	**27.671**	**34.579**
Pattern response	**-3.582**	**-2.047**	**-2.047**	**0.042**	**-7.036**	**-0.127**
Conditions	**2.077**	**3.087**	**3.087**	**0.002**	**0.749**	**3.406**
Pattern response x Conditions	0.168	0.249	0.249	0.804	-1.161	1.496

Note. (a) Scatterplot of pattern expressions during exclusion and inclusion. (b) Scatterplot regression line of whole-brain pattern expression and loneliness. (c) Multiple regression results predicting loneliness from whole-brain pattern expressions. (d) Multiple regression with interaction term 'pattern response x conditions' testing whether the coefficients of pattern responses during exclusion and inclusion are significantly different.

We also investigated whether pattern response in certain functional networks predict loneliness better than others. By calculating pattern expression within voxels consisting each network, we examined the relationship of pattern expression in three functional networks (mentalizing network, amygdala network, social pain network) with loneliness. None of the individual pattern expression of networks during exclusion and inclusion were associated with loneliness (Supplementary Table S1).

Additionally, pattern expressions during exclusion and inclusion were not different between individuals who reported stronger behavioral response to social exclusion, i.e. feeling excluded, ignored or hurt. They were also not related to the contextual factors of the task, i.e. average communication or closeness with other players. These contextual factors of the task did not moderate the relationship between pattern responses and loneliness. Finally, they were not associated with other psychological states, such as depression, perceived stress, anxiety, or extraversion personality (Supplementary Table S2).

Chapter 4. Discussion

Social isolation is an important risk factor to the health of older adults and understanding the psychological and neurophysiological processes that regulate the feeling of loneliness is an essential step towards developing effective interventions for loneliness. Social exclusion is a specific incident of social isolation that can induce different levels of reactivity to social cues and may be related to the general feeling of loneliness. In this study, we aimed to understand the neural mechanisms of social exclusion using MVPA and their individual differences related to loneliness.

We identified a neural pattern signature of social exclusion in older adults based on fMRI responses to exclusion and inclusion during Cyberball task. This pattern discriminates social exclusion from inclusion with 0.632 accuracy and 0.693 AUC. The regions with the highest peak voxel weights include the bilateral IPL and temporal pole of the mentalizing network, and amygdala and ventral striatum of the amygdala network. Feature importance analysis showed that the regions contributing most to the prediction were the dmPFC, right temporal pole, right IPL, and precuneus of the mentalizing network, left amygdala and left ventral striatum of the amygdala network, and right anterior insula of the social pain network. Thus, primarily the regions of the mentalizing and amygdala network play important roles as the neural mechanisms of social exclusion. These results may imply that psychological functions related to these regions are involved during social exclusion experience.

The regions of the mentalizing network, including IPL, temporal pole, dmPFC, and precuneus, are related to the ability to infer one's own and others' state of mind. During social exclusion, these regions may support the process of considering intentions of the individuals who are excluding the participant in the social event or

the process of internal ruminations about the relevance of potential ongoing exclusion for broader social relations (Amodio & Frith, 2006; Schmälzle et al., 2017). The amygdala network, including the amygdala, lateral OFC, ventral striatum, and vmPFC, is related to various social relationship characteristics and emotional values. The amygdala is considered the hub of the social brain, sharing anatomical and functional connections with almost every other brain region implicated in social cognition. The vmPFC and ventral striatum is involved in processes related to motivating prosocial or affiliative behaviors. Lateral OFC supports perception and sensory processes involved in detecting, decoding, and interpreting social signals from others in the context of past experience and current goals (Bickart et al., 2014). These regions also support the function of processing affective value and motivational significance of various stimuli, including other people (Zerubavel et al., 2015).

In this study, the social pain network consisting dACC and anterior insula contributed relatively less to the prediction of social exclusion in this study. This network is identified to be associated with distress during exclusion (Eisenberger et al., 2003; Rotge et al., 2015). These differing findings may reflect differences in methodology. The role of dACC in social cognition has mainly been studied via analyses of single univariate activation effects and these studies have shown rather inconsistent results (Cacioppo et al., 2013). However, it is also possible that the subtle experience of being ignored by others may not have been such a strong painful experience for our participants, thus eliciting less involvement of distress functions. In fact, our participants did not report strong negative reactions to being excluded (i.e. feeling ignored, feeling hurt) during the virtual ball-tossing task, which may be attributed to the fact that many of them were older adults (mean age of 71) living in

rural neighborhoods with relatively few years of education. The participants may have processed and responded to the experience of social exclusion to a subtle degree such that neural systems involved in distress as well as behavioral responses of distress were not elicited. It has also been suggested by some studies that regions of the social pain network (dACC and anterior insula) are commonly involved in processing social exclusion and inclusion (Dalgleish et al., 2016; Simard et al., 2018), in which case activations in these regions may not contribute to distinguishing the two conditions.

These results are compatible with another study using MVPA analysis on identifying the neural mechanism of social rejection (Woo et al., 2014). The study found that an fMRI classifier distinguishing ex-partner versus friend was supported by increased activity in mentalizing network regions (dmPFC, right temporal parietal junction(TPJ), precuneus) and other regions associated with negative emotion and its regulation (thalamus, supplementary motor area, inferior frontal gyrus). In our study, we also found the contribution of mentalizing regions to the prediction of social exclusion, and additionally found that amygdala network regions were important. Indeed, social rejection induced by thinking about a break-up experience with one's ex-partner is different from social exclusion during Cyberball, and thus different types of social situations may involve different brain mechanisms. However, it is notable that regions of the mentalizing network have been commonly associated in the studies, suggesting that the mentalizing function is a non-negligible factor of social isolation.

Examining loneliness-related individual differences in pattern response showed that lonely individual had higher pattern response to social exclusion but not inclusion. Previous studies on social cognitive factors of loneliness have indicated

that loneliness can trigger implicit hypervigilance for social threats, which in turn produces attentional, confirmatory, and memory biases (Cacioppo & Hawkley, 2009). The increased neural reactivity to social exclusion in lonely adults may represent hyper-sensitivity to social situations that as perceived as threats to one's social connectedness. The neural responses may capture sensitivity to social exclusion that was not explicitly manifested as behavioral responses. When examining the specificity of the neural response, individual network-level pattern responses during exclusion and inclusion were not related to loneliness. In other words, not the contribution of one specific functional network was enough to predict loneliness. This result indicates that the integration of three distinct functional networks as a whole is important in predicting the loneliness outcome, confirming the previous assumption that neural patterns of social isolation are widely distributed in the brain (Kragel et al., 2015; Saarimaki et al., 2016). Finally, neural pattern responses to social exclusion was not associated with behavioral responses to exclusion (i.e. feeling excluded, ignored, hurt), contextual factors of exclusion (i.e. relationships with other players), and other psychological states (i.e. depression, anxiety, perceived stress). These results demonstrate that the neural signature response to social exclusion is specific to the feeling of loneliness.

The results of the current study have theoretical and practical implications. To our knowledge, this is the first study to investigate the neural mechanisms of social exclusion using MVPA to attain the distributed neural patterns representing complex psychological processes underlying a subtle incident of social isolation, i.e. social exclusion. Also, the importance of the mentalizing network and amygdala network as neural mechanisms of social exclusion suggests that the ability to deduce the mental states of self and others along with the sensitivity to social and emotional

values supports the experience of social exclusion. The results that lonely adults exhibit higher neural reactivity to social exclusion provide evidence to the social cognition framework of loneliness (Cacioppo & Hawkley, 2009). This line of basic research may be informative for developing interventions for chronically lonely adults, such as cognitive behavioral therapy tackling maladaptive social cognition that begets hyper-reactivity to social threats (Masi et al., 2011).

Several limitations should be noted. As the development of decoding models is an ongoing process, models with higher classification performance needs to be developed and generalizability of the identified signature must be attested on other samples of older adults. Also, further investigation on the chronicity of loneliness can provide stronger support for the social cognition framework of loneliness. Although we found no relationships between the neural signature response and behavioral responses to social exclusion, other measures of behavioral responses must be further explored, e.g. other emotional responses, self-preservation tendency, or memory biases of the negative aspects of the situation. Moreover, the currently identified pattern signature consists of *a priori* regions that are known to be related to social cognition and behavior, especially social isolation. As other brain regions with various functions that are yet known to be related may also play part in processing the social exclusion experience, we need to compare the current model with models including other regions of the brain. Finally, the identified pattern signature captures the overall brain mechanisms of social exclusion and does not take into account the effect of contextual factors (i.e. relationships with players). It remains future work to examine the differences in pattern reactivity related to the specific situational characteristics of social exclusion.

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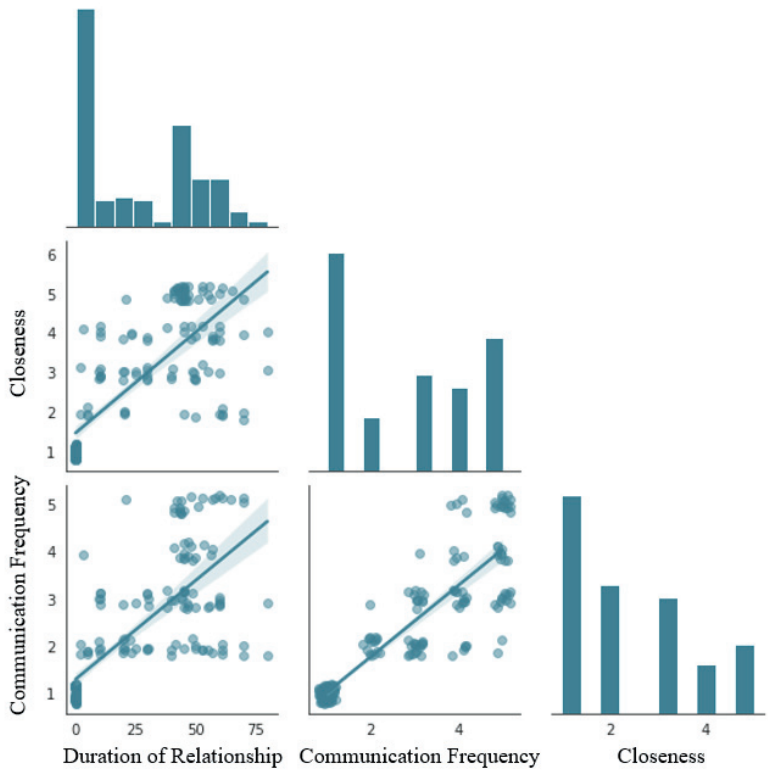
Appendix

Supplementary Figures and Tables

Figure S1.

Relationships with Two Other Players of the Cyberball.

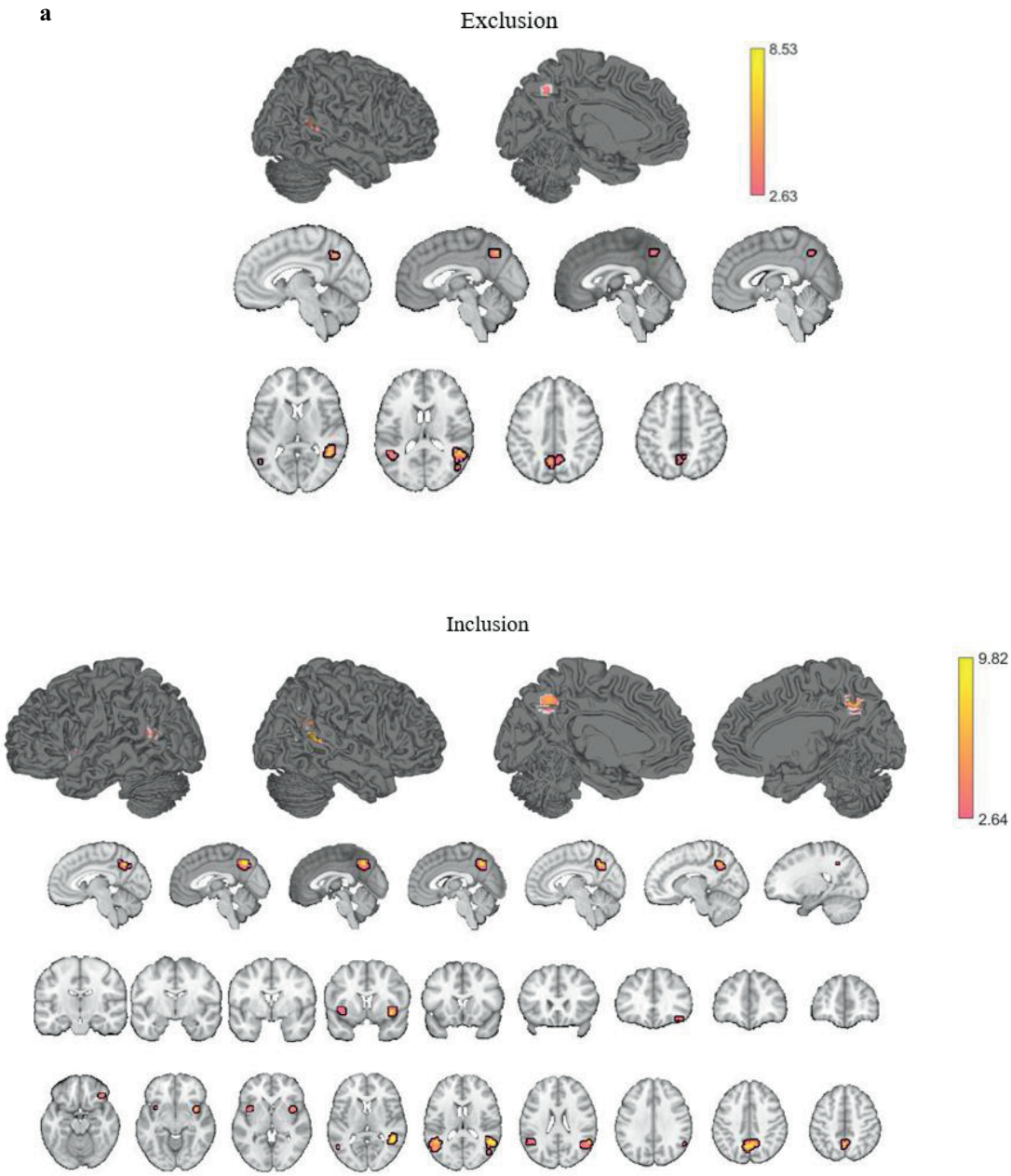


Note. The diagonal figures are histograms of each variable and other figures are scatterplots of each pair of variables.

Figure S2.

Group-level analysis of brain activations during the Cyberball

a



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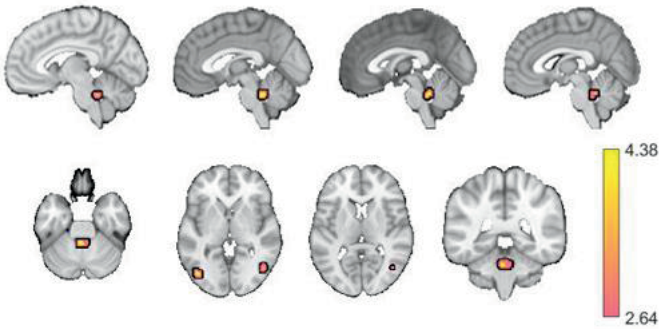

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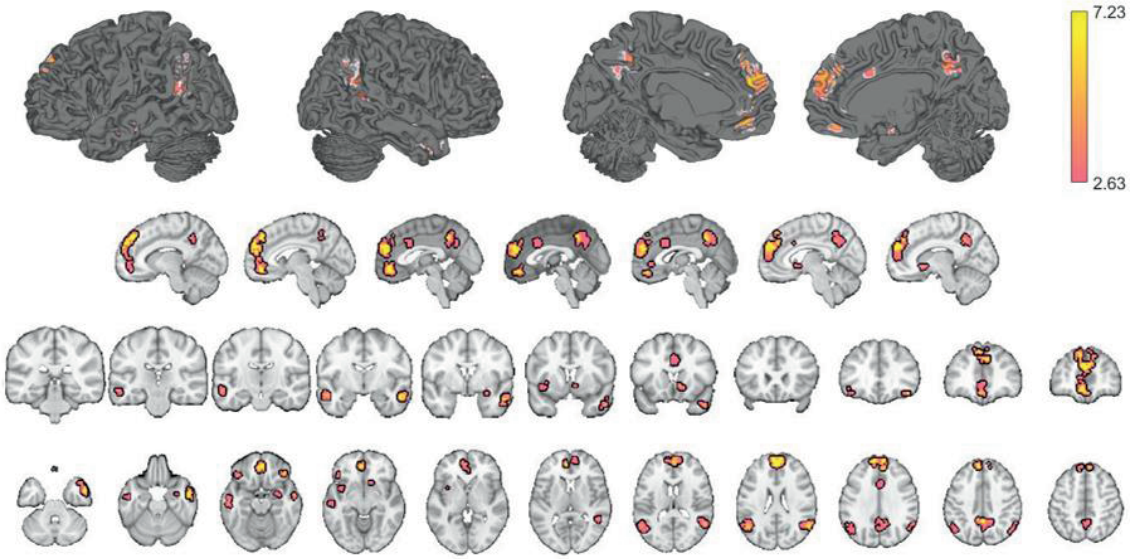

b Contrast	Region	Cluster size	MNI Coordinates			Peak T-score
			x	y	z	
Exclusion	Middle temporal gyrus (R) Inferior occipital gyrus (R) Middle occipital gyrus (R) Angular gyrus (R)	295	50	-64	10	8.53
	Precuneus (L, R)	119	-4	-64	44	4.96
	Middle temporal gyrus (L) Angular gyrus (L)	64	-46	-60	10	4.70
Inclusion	Middle temporal gyrus (R) Inferior occipital gyrus (R) Middle occipital gyrus (R) Angular gyrus (R)	511	50	-64	10	9.82
	Precuneus (L, R)	390	8	-56	44	7.42
	Middle temporal gyrus (L) Angular gyrus (L) Middle, inferior occipital gyrus (L)	290	-50	62	12	7.32
	Anterior insula (R) Posterior insula (R) Putamen (R)	99	36	10	-8	6.58
	Anterior insula (L) Frontal operculum (L)	54	-36	12	-6	4.02
	Lateral, posterior orbital gyrus (R) Inferior frontal gyrus (orbital part) (R)	26	38	34	-12	5.48
Exclusion > Inclusion	4th Ventricle Brain stem Cerebellum (L)	82	-2	-44	-28	4.38
	Inferior occipital gyrus (L) Middle temporal gyrus (L)	65	-42	-74	0	3.93
	Inferior occipital gyrus (R) Middle temporal gyrus (R)	44	46	-68	2	3.44
Inclusion > Exclusion	Superior frontal gyrus medial segment (L, R)	1039	-2	40	44	7.23
	Superior frontal gyrus (L)	31	10	44	44	5.65
	Middle Temporal Gyrus (R) Superior temporal gyrus (R)	245	52	-4	-22	6.76
	Medial frontal cortex (L, R) Anterior cingulate (L)	241	-6	44	-12	5.94
	Precuneus (L, R) Posterior cingulate (L, R)	449	-2	-46	40	5.91
	Angular gyrus (R) Middle occipital gyrus (R)	503	54	-60	26	5.24
	Caudate (R) Lateral ventricle (R) Accumbens (R)	40	8	16	-2	5.19
	Lateral, posterior orbital gyrus (R) Inferior frontal gyrus (orbital part) (R)	29	42	34	-14	5.14
	Inferior frontal gyrus (L) Lateral orbital gyrus (L)	31	-44	34	-8	4.71

Note. (a) The contrast maps of Exclusion, Inclusion, Exclusion>Inclusion, Inclusion>Exclusion conditions using the standard General Linear Model (GLM) analysis across all participants (n=88), thresholded at p<.005 (uncorrected, cluster size>20), as suggested by Lieberman & Cunningham (2009). All maps were masked by the *a priori* mask of social cognition and behavior, except for the [exclusion>inclusion] contrast which was analyzed at the whole-brain level. (b) Regions from the contrasts with the same thresholds.

Table S1.

Correlations between Network-level Pattern Responses and Loneliness.

Network-level Pattern Response		r	*p*
Mentalizing network	Exclusion	-.033	.763
	Inclusion	-.005	.967
Amygdala network	Exclusion	.071	.508
	Inclusion	.001	.993
Social pain network	Exclusion	-.029	.791
	Inclusion	-.033	.763

Table S2.

Relationships between Whole-brain Pattern Responses and Other Variables.

a

Variables		Pattern response during exclusion		Pattern response during inclusion	
		r	*p*	r	*p*
Behavioral response to exclusion	Feeling excluded	.016	.883	.182	.092
	Feeling ignored	-.034	.754	-.152	.163
	Feeling hurt	.064	.555	-.053	.624
Relationships with players	Average communication	.155	.149	-.046	.669
	Average closeness	-.156	.148	-.051	.636
Psychological factors	Depression	.171	.111	-.026	.808
	Perceived stress	.077	.477	-.079	.466
	Anxiety	.039	.720	-.038	.727
	Extraversion	.030	.784	.105	.330

b

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**38.095**	**9.385**	**4.059**	**0.001**	**19.433**	**56.758**
Pattern response during exclusion	0.123	2.283	0.539	0.957	-4.417	4.663
Average closeness	-4.343	3.746	-1.159	0.250	-11.793	3.107
Pattern response x Average close	0.884	0.946	0.934	0.353	-0.998	2.765

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**24.196**	**5.135**	**4.712**	**0.000**	**13.985**	**34.408**
Pattern response during exclusion	**3.019**	**1.242**	**2.431**	**0.017**	**0.549**	**5.489**
Average communication	1.214	1.469	0.827	0.411	-1.707	4.136
Pattern response x Average comm	-0.264	0.324	-0.813	0.419	-0.909	0.381

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**36.759**	**3.544**	**10.371**	**0.000**	**29.709**	**43.805**
Pattern response during inclusion	3.241	2.656	1.221	0.226	-2.039	8.521
Average closeness	-0.787	1.420	-0.554	0.581	-3.610	2.037
Pattern response x Average close	-0.669	1.144	-0.584	0.561	-2.944	1.607

Variable	Beta	*SE*	*t*	*p*	95% CI	
					LL	*UL*
Intercept	**32.976**	**2.026**	**16.273**	**0.000**	**28.947**	**37.006**
Pattern response during inclusion	**2.987**	**1.477**	**2.010**	**0.048**	**0.031**	**5.904**
Average communication	0.780	0.628	1.243	0.217	-0.468	2.029
Pattern response x Average comm	-0.510	0.475	-1.074	0.286	-1.456	0.435

Note. (a) Correlations between loneliness and other variables, including behavioral responses to social exclusion, contextual factors of the Cyberball, and other psychological factors. (b) Moderation effects of contextual factors of social exclusion (relationships with two players) on the relationship between pattern response and loneliness.

국문 초록

사회적 배제의 신경반응패턴과 노년기 고독감의 관계

사회적 고립은 노년기 정신 건강과 신체 건강에 영향을 미치는 주요요인이다. 그 중 사회적 배제는 다른 사람으로부터 무시되거나 주목 받지 못하는 구체적인 사회적 고립 경험이다. 사회적 존재로서 인간의 뇌는 유익한 사회적 관계를 형성하고 유지하는 기능을 한다. 사회적 배제의 신경기전을 이해하면 사회적 배제 경험과 관련된 심리기제에 대한 통찰을 얻을 수 있다. 또한, 사회적 배제의 신경반응패턴과 고독감의 관계를 확인함으로써, 고독감이 만성적으로 유지되도록 하는 사회인지 특성을 이해할 수 있다. 본 연구는 가상의 공놀이 게임(Cyberball) 과제 중 신경활성화의 다변량 패턴분석을 통해 한국 노인 샘플에서 사회적 배제의 신경반응패턴을 찾았다. 또한, 발견된 사회적 배제의 신경반응패턴이 고독감과 관련된 개인차를 보이는지 확인했다. 88명의 한국 노인을 대상으로 과제 중 신경활성화로 사회적 배제조건과 참여조건을 구분하는 예측모델을 개발했으며, 이 모델은 정확도 0.632, AUC 0.693의 예측력을 보였다. 복셀과 영역의 예측자 중요도를 분석한 결과, 모델의 예측에 가장 많이 기여한 영역은 양측 하두정소엽, 배내측 전전두피질, 설전부, 편도체, 복측선조체였다. 이 영역은 마음을 추론하는 능력과 관련된 mentalizing 네트워크 그리고 편도체를 중심으로 연결된 amygdala 네트워크에 속한다. 또한, 평소 고독감을 높게 지각할수록 사회적 배제 경험 시에 높은 신경반응성을 보였다. 본 연구는 사회적 배제의 신경반응성이 다양한 사회적 기능을 하는 영역에 넓게 분산된 형태의 패턴을 보이며, 고독감을 많이 느끼는 노인은 사회적 배제 상황에 더 민감하게 반응하는 특성이 있음을 확인했다. 한국 노인 샘플에서 사회적으로 배제되는 고립 경험 시에 사용되는 인지적 특성에 대한 이해를 제공하고, 고독감에 대한 개입 시 사회인지 특성에 초점을 두는 개입방법의 중요성을 시사한다.

주요어 : 사회적 배제, 고독감, 다변량 패턴분석(MVPA), 노년기

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