

RESEARCH ARTICLE

A neuroimaging study of interpersonal distance in identical and fraternal twins

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Funding information

Riksbankens Jubileumsfond, Grant/Award Number: P20-0125; Vetenskapsrådet, Grant/Award Numbers: 2014-01160, 2018-01322; Bank of Sweden Tercentenary Foundation; Swedish Research Council

Abstract

Keeping appropriate interpersonal distance is an evolutionary conserved behavior that can be adapted based on learning. Detailed knowledge on how interpersonal space is represented in the brain and whether such representation is genetically influenced is lacking. We measured brain function using functional magnetic resonance imaging in 294 twins (71 monozygotic, 76 dizygotic pairs) performing a distance task where neural responses to human figures were compared to cylindrical blocks. Proximal viewing distance of human figures was compared to cylinders facilitated responses in the occipital face area (OFA) and the superficial part of the amygdala, which is consistent with these areas playing a role in monitoring interpersonal distance. Using the classic twin method, we observed a genetic influence on interpersonal distance related activation in the OFA, but not in the amygdala. Results suggest that genetic factors may influence interpersonal distance monitoring via the OFA whereas the amygdala may play a role in experience-dependent adjustments of interpersonal distance.

KEYWORDS

amygdala, emotion, fMRI, fusiform face area, heritability, occipital face area, personal space, SCR

1 | INTRODUCTION

Social spacing is an evolutionary conserved behavior that can be observed in social species including humans. The behavior is thought to reduce aggressive encounters and spread of diseases (Giuggioli et al., 2013) between members of a species, thus promoting survival (Curtis, 2014; McBride, 1971). Individual differences in social spacing depends on learning (Åhs et al., 2015) but could also be expected to be under genetic influence, given its evolutionary origin (Waser & Wiley, 1979). We here aimed to establish what brain areas respond to proximal interpersonal distance and

whether activity in these areas is genetically influenced, in a large sample of twins.

Across neuroimaging studies, social stimuli consistently activate a network of regions situated within the visual stream. This network of brain regions includes the lateral occipital face area (OFA) in the inferior occipital lobe and the fusiform face area in the fusiform gyrus (Grill-Spector et al., 2017; Kanwisher et al., 1997). In addition, the amygdala is consistently activated by social stimuli (Åhs et al., 2014; Fusar-Poli et al., 2009). Although there is great consistency in the set of brain regions activated by social stimuli, the magnitude of the responses in these areas varies between individuals. The source of

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individual variation in activation to social stimuli in the fusiform face area has been suggested to be partially genetic, as a study found greater correlation between identical than fraternal twin pairs in this area (Polk et al., 2007b). Using a larger sample of twins from the Human Connectome Project, the finding of a genetic influence in face-related activation of the fusiform face area has been replicated (Abbasi et al., 2020). Genetic influences on activation serving face perception were also observed in the lateral OFA (Abbasi et al., 2020).

Whereas social stimuli activate brain areas mostly in the ventral visual stream, brain activations to proximal relative to distant objects have been found in the primary visual cortex (visual area V1) extending in the dorsal visual stream up to the parietal lobe (Vieira et al., 2017; Vieira et al., 2019). The amygdala has also been found to be activated by objects suddenly appearing in a proximal location (Coker-Appiah et al., 2013; Vieira et al., 2019). Apart from the amygdala, the hippocampus and entorhinal cortex could also be hypothesized to be relevant to distance perception given their role in spatial mapping of the environment (Rigoli et al., 2016; Suarez-Jimenez et al., 2018).

Brain systems monitoring social information and proximity to objects interact to monitor interpersonal space. Research on neural correlates of interpersonal distance indicate that ventral parietal (Holt et al., 2014) and lateral occipital areas increase their activity to social stimuli at near distance (Vieira et al., 2017). A study in a patient with lesions of the bilateral amygdala also suggest that this area monitors personal space (Kennedy et al., 2009). The amygdala is also regulating defensive responses, and increases in autonomic activity and startle-responses to social stimuli appearing at near interpersonal distance have been reported (Ahs et al., 2015; Graziano & Cooke, 2006; McBride et al., 1965; Rosén et al., 2017; Wilcox et al., 2003). The genetic influence on brain responses supporting interpersonal space perception or autonomic activation from proximal encounters is, however, yet to be determined.

The aim of the present study was to investigate the genetic influence on brain function supporting visual processing of social content, distance, and interpersonal distance. To accomplish this, we developed a functional magnetic resonance imaging (fMRI) paradigm probing brain response to social and proximal objects in a sample of 71 monozygotic (MZ) and 76 dizygotic (DZ) adult twin pairs recruited from the Swedish Twin Registry. During the experiment, we displayed humanoid characters and cylinder-shaped objects on a screen in the scanner (Figure 1). Characters and objects were displayed at proximal and distal distances. Brain responses to social objects were assessed by comparing presentation of humanoid characters to cylindrical shapes. We compared proximal and distant presentations to determine distance-related brain responses. Activation to interpersonal distance was defined as the interaction between social content and distance. Specifically, we were interested in brain areas that showed greater responses to near social than nonsocial stimuli relative to their distant counterparts. Brain activity was measured using fMRI and autonomic activity was indexed by skin conductance responses (SCRs). We have previously shown that SCR is sensitive to distance

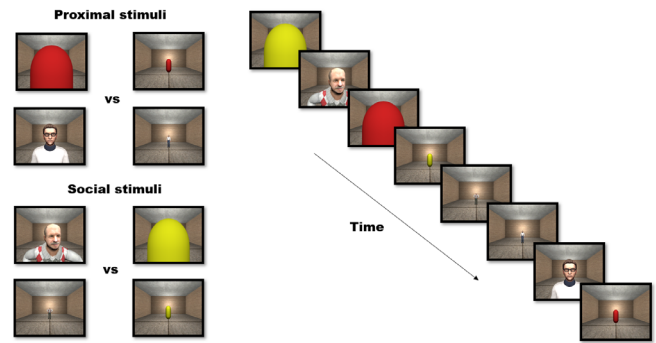


FIGURE 1 Experimental design. Images depict stimuli used to test brain and autonomic responses to social content and viewing distance. Interpersonal distance was defined as the interaction between social content and distance. Human figures and cylinders of similar size were presented 10 times each at proximal and distant locations for a total of 40 presentations (2 distances \times virtual characters and 2 distances \times cylinders)

manipulations in immersive virtual reality as well as on a flat screen (Rosén et al., 2017; Rosén et al., 2019). The brain was parcellated according to the Julich Brain Atlas (Amunts et al., 2020) which is based on cytoarchitectonic definitions of brain areas. A region of interest (ROI) approach was used as this is known to improve signal to noise ratio in fMRI. We hypothesized a genetic influence on brain function in areas of the ventral visual stream consistent with previous reports (Abbasi et al., 2020; Polk et al., 2007a). We also expected a genetic influence on brain responses related to viewing distance and interpersonal distance, although we did not have specific hypotheses in which brain areas effects would be observed.

2 | MATERIALS AND METHODS

2.1 | Subjects

During 2017–2018, same sex twins between ages 20 and 60 were recruited through the Swedish Twin Registry. A total of 3021 individuals were invited to participate in the study via mail, and out of those, 646 applicants signed up for participation. Participants were excluded if they were unable to undergo an MRI examination safely because of medical implants or other nonremovable metal inside the body, ongoing substance abuse, ongoing psychological treatment, and/or use of medicine affecting emotion or cognition. After the initial screening, 305 participants underwent fMRI. After data collection, 11 participants were excluded because of excessive head motion (3), inadequate performance on the experimental task (5), or missing data or incomplete twin pair (3). The final sample of 294 twins included 71 MZ pairs (42 female and 29 male pairs), 76 DZ pairs (44 female and 32 male pairs; mean age 33.64 years; $SD = 10.13$, age range: 20–58 years; See Table S1 for demographical characteristics of the twin sample). Participants received 1000 SEK (roughly equal to 100 USD) as reimbursement for their participation. All participants included in the study

provided written informed consent. The study was approved by the Uppsala Ethical Review Board (Dnr2014-01160).

2.2 | Materials

2.2.1 | Stimuli and virtual environment

Two male humanoid characters, two cylinder-shaped objects, and one virtual environment were created in Unity (version 5.2.3, Unity Technologies, San Francisco, CA) (Figure 1). To control for potential confounds based on stimuli sizes, we modeled the two cylinder-shaped objects to match the size of the two humanoid characters. Two stimuli of each type (social vs. nonsocial) was used to maximize the delay of habituation. The virtual environment in which characters and cylinders was presented consisted of a room with four sand-colored brick walls, gray concrete roof, and a wooden or concrete floor.

2.3 | Stimulus presentation software

Contexts and stimuli were presented on a flat screen in the MR scanner with the help of a projector (Epson EX5260). The computer controlling the stimulus presentation ran a custom-made software created in Unity (version 5.2.3, Unity Technologies, San Francisco, CA) and communicated with BIOPAC (BIOPAC Systems, Goleta, CA) through a parallel port interface. The software for the parallel port interface was custom-made and used standard .NET serial communication libraries by Microsoft (Microsoft Corporation, Albuquerque, New Mexico). Stimulus presentation software can be obtained upon request.

2.4 | Brain imaging

Imaging data were acquired using a 3.0 T scanner (Discovery MR750, GE Healthcare) and an 8-channel head-coil at Karolinska Institute Center for Radiology Research in Stockholm, Sweden. Foam wedges, earplugs, and headphones were used to reduce head motion and scanner noise. T1-weighted structural images were acquired with whole-head coverage [repetition time (TR) = 6400 ms, echo time (TE) = 28 ms, acquisition time 6.04 min, and flip angle 11°]. Functional images were acquired using gradient echo-planar-imaging (EPI), with TR = 2390 ms, TE = 28 ms, flip angle = 80°, slice thickness 3.0 mm with no spacing, axial orientation, frequency direction R/L, and interleaved bottom up. Higher order shimming was performed and the number of dummy scans before the experiment was five. Total number of slices for every acquired volume was 47 with a voxel size of 3.0 mm³.

2.5 | Skin conductance responses

Skin conductance recording was controlled with the MP-150 BIOPAC system (BIOPAC Systems, Goleta, CA). Radio-translucent disposable

dry electrodes (EL509, BIOPAC Systems, Goleta, CA) were coated with isotonic gel (GEL101, BIOPAC Systems, Goleta, CA) and placed on the palmar surface of the left hand. The signal was high-pass filtered at 0.05 Hz and SCRs were scored using Ledalab (Benedek & Kaernbach, 2010) software package implemented in Matlab 2018 (Mathworks, Inc., Natick, MA). SCR was scored using the maximum phasic driver amplitude 1–4 s after stimulus presentation for each participant. SCRs were range-corrected by dividing all SCRs for each participant with each participants average SCR (Ben-Shakhar, 1985).

2.6 | Procedure

2.6.1 | Interpersonal distance task

The task used was developed to study psychophysiological and neural responses to social stimuli viewed at proximal and distant distances (Rosén et al., 2017). One virtual character or object was presented at a simulated distance of 0.3 m (Proximal) or 2.7 m (Distant) by a projector, projecting an image to the participant on a screen in the MR scanner (Figure 1). The distances were selected to match distances corresponding to inside and outside personal space (Kennedy et al., 2009). Each stimulus presentation lasted 6 s with an inter-stimulus interval (ITI) ranging between 8 and 12 s. During the ITI, the virtual room in which the character or object was presented was still shown on the screen. To control for ordering effects, which could be large for fMRI and SCR data, two different stimulus presentation orders were counterbalanced across participants. The two presentation orders differed only in the first four presentations, where the order was reversed for half of the participants. Presentation orders were pseudo-randomized, so that no more than two consecutive presentations of each stimulus type occurred. Each twin in a pair was given the same presentation order. The total number of presentations were 40, which included 10 presentations of a virtual character at 0.3 m, 10 presentations of a virtual character at 2.7 m, 10 presentations of a cylinder at 0.3 m, and 10 presentations of a cylinder at 2.7 m. Total time for the experimental task was 10 min and 4 s. The current study was part of a larger study where the participants spent a total of 60 min in the fMRI scanner. The social content and distance presentation task was the first experimental run. Following the interpersonal distance task, participants performed a fear-conditioning task (Kastrati et al., 2021) and a face-matching task. Information about the other experimental runs is available at the Open Science Foundation (OSF) repository for this project (<https://osf.io/7dz9/>).

2.7 | Statistical analysis of imaging data

Analyses of fMRI-data were performed using SPM12 (Wellcome Department of Cognitive Neurology, University College, London) implemented in Matlab 2019a (Mathworks, Inc., Natick, MA). Preprocessing of images were performed using interleaved slice time correction and included re-alignment and co-registration to the

anatomical T1-weighted image. Images were spatially normalized to Montreal Neurological Institute (MNI) standard space. Normalized images were smoothed with an 8 mm FWHM Gaussian kernel.

Statistical analysis included a voxel-based first-level analysis and a ROI-based second-level analysis. First-level analysis used event-related modeling in the SPM12 software. Trial onsets for the characters and cylinders displayed at proximal and distant distances were modeled as four separate regressors with a trial duration of 6 s. Realignment parameters were included as six regressors in the design matrix to correct for head movements during image acquisition. Regressors were convolved with a hemodynamic response function. Contrast images for each participant were computed for the three contrasts (1) social greater than cylinder, (2) proximal greater than distant, and (3) the interaction between social content and distance (interpersonal distance).

In the group-level analysis, we used simple *t*-tests whether the contrast estimate for each ROI was different from zero. Mean contrast estimates for every ROI was extracted with the help of the `spm_read_vols()` function implemented in SPM12. We then performed *t*-tests on all extracted ROI estimates in R (R Core Team [2013], <http://www.R-project.org/>). This was performed for all contrasts (social content, distance, and interpersonal distance). We also analyzed proximal and distant presentations for social content and distance separately to control for interactions and effects of distance on social presentations. The level of significance was set to $p < .05$ (Bonferroni-corrected).

Extraction of mean contrast estimates was performed using the Julich Brain Atlas implemented in SPM Anatomy toolbox v.2.2c (Eickhoff et al., 2005), which is based on cytoarchitectonic differences between brain areas. The choice of using the cytoarchitectonic Julich Brain Atlas for parcellation of contrast images was based on previous findings showing that gene expression differs along a posterior–anterior gradient in the visual stream across these regions (Gomez et al., 2019). The Julich Brain Atlas contains 200 cytoarchitectonic masks. All ROIs but two were used. These two ROIs were located outside the activated brain region in the group-level analysis (Cerebellum VIIa crus1 Verm L and Cerebellum VIIa crus1 Verm R) and no fMRI data could hence be extracted. The choice of ROIs was therefore unbiased, as ROI definitions were independent of our study.

2.8 | Statistical analysis of SCR

We analyzed SCR data using simple *t*-tests implemented in R. Social (humanoid character vs. cylinders-shaped object) and proximal (proximal vs. distant trials) stimuli was compared. For the interaction between social content and distance, we analyzed SCR by comparing change scores between proximal and distant trials for social and non-social stimuli. The level of statistical significance was set to $p < .05$.

2.9 | Sensitivity analysis

We performed statistical analyses of fMRI and SCR data to evaluate if results could be attributed to differences between men and women. To evaluate if responses differed between men and women, we performed two-sample *t* tests.

2.10 | Estimation of genetic influences on brain function

Identification of outliers: Before the genetic modeling, we identified univariate outliers in our sample to increase the robustness of the estimated correlations between MZ and DZ twins. Removal of outliers is recommended in samples of less than 200 individuals (Pernet et al., 2013) and has previously been used in a neuroimaging study of twins performing a working memory task (Blokland et al., 2011). Identification and exclusion of outliers was performed for all contrasts (social content, distance, and interpersonal distance) and each ROI prior to the analysis. We visualized outliers using boxplots in R and removed any participant with a mean contrast estimate or skin conductance response deviating more than 1.5 times the interquartile range above the upper and lower quartile. If one twin of a twin-pair was categorized as outlier, the co-twin was also excluded from the statistical analysis.

Estimation of genetic effects: After outliers were excluded, additive genetic influences of brain data and SCR were estimated using the Mets software package (Holst et al., 2016; Scheike et al., 2014) implemented in R. We modeled data by decomposing sources of variation in contrast estimates from the analysis of fMRI data and SCR into the factors additive genetic (A), common environment (C), and nonshared environment and error (E). The A, C, and E factors were estimated by contrasting MZ-twin pair correlations with DZ-twin pair correlations. The A-factor could be identified based on that MZ-twins were genetically identical while DZ-twins shared 50% of their co-segregating alleles. Additionally, we assume that a shared environmental contribution (C) is equally shared within pairs regardless if they are MZ- or DZ twins. Finally, unique variance was estimated as an E-factor, and represented unique individual experiences and error. The A, C, and E factors were estimated for each of the 198 ROIs in each of the three contrasts (social content, distance and interpersonal distance).

2.11 | Genetic influence

2.11.1 | Genetic influence on neural responses to social content

The variance in neural responses to social content in each ROI was partitioned into additive genetics (A), common environment (C), and unique environment (E) (ACE model). Statistically significant genetic (A) influences on brain responses (Bonferroni-corrected $p < .05$) were observed in the lateral OFA of the inferior occipital gyrus (Visual h0c4v) and the fusiform face area (FG4), Table 1 and Figure 2. We found no statistically significant genetic influence in the amygdala related to social content. To increase robustness of our analysis, we also combined the amygdala subregions of the Julich brain atlas into one left and one right amygdala ROI. We found no significant genetic influence activation in the left or right amygdala using these combined ROIs.

2.11.2 | Genetic influence on neural responses tracking distance

We found ROIs with statistically significant estimates of additive genetic influence on neural activity tracking distance (Bonferroni-corrected $p < .05$) located in the calcarine and lingual gyri (Visual hOc2, hOc4v, and hOc3d), which included primary visual cortex (V1) (Table 1 and Figure 2). However, we found no statistically significant genetic influence in the amygdala subregions or in the combined left and right amygdala ROIs, that included all subregions.

2.11.3 | Genetic influence on neural responses showing an interaction between social content and distance

We found a statistically significant genetic influence on contrast values from the interaction between social content and the distance

manipulation in an area consistent with the OFA in the middle occipital gyrus (Visual hOc3v), Table 1 and Figure 2.

Because signals scale with the variance in biological systems, we wanted to know whether genetic influences only were observed in ROIs with large variance. To this end, we plotted the mean contrast value across participants for each ROI against the variance in contrast values for the same ROI (Figure 3) and marked ROIs with a significant genetic influence on contrast values. In the plots, genetic influences were observed in ROIs with both low and high variance. Therefore, the observed genetic influences were not restricted only to ROIs with large variance.

2.11.4 | Genetic influence on SCR

Genetic and environmental influences on SCR were also determined. We found that the genetic influence on SCR to distance was not statistically significant ($MZ_n = 62$, $DZ_n = 71$, $A = 0.00$, $n.s.$; $C = 0.00$, $n.s.$). The genetic influence on SCR to social stimuli was also not

TABLE 1 Brain regions with additive genetic influence (A) on brain function surviving the statistical criterion (Bonferroni-corrected $p < .05$) for social content, distance and interpersonal distance

| Region | MZ-pairs | DZ-pairs | MZ _r | DZ _r | A | A 95% CI lower | A 95% CI upper | C | C 95% CI lower | C 95% CI upper | E | E 95% CI lower | E 95% CI upper |
|-------------------------------|----------|----------|-----------------|-----------------|------|----------------|----------------|------|----------------|----------------|------|----------------|----------------|
| <i>Social content</i> | | | | | | | | | | | | | |
| Visual FG2 R | 63 | 69 | 0.43 | 0.07 | 0.35 | 0.15 | 0.55 | 0.00 | 0.00 | 0.00 | 0.65 | 0.45 | 0.85 |
| SPL 5 Ci R | 59 | 70 | 0.34 | 0.03 | 0.28 | 0.07 | 0.49 | 0.00 | 0.00 | 0.00 | 0.72 | 0.51 | 0.93 |
| Visual FG1 R | 57 | 69 | 0.27 | 0.06 | 0.26 | 0.05 | 0.48 | 0.00 | 0.00 | 0.00 | 0.74 | 0.52 | 0.95 |
| Visual hOc5 R | 63 | 71 | 0.30 | 0.11 | 0.26 | 0.06 | 0.46 | 0.00 | 0.00 | 0.00 | 0.74 | 0.54 | 0.94 |
| Visual hOc4v L | 64 | 71 | 0.22 | 0.12 | 0.23 | 0.01 | 0.45 | 0.00 | 0.00 | 0.00 | 0.77 | 0.55 | 0.99 |
| <i>Distance</i> | | | | | | | | | | | | | |
| Visual hOc2 R | 63 | 71 | 0.34 | 0.12 | 0.30 | 0.10 | 0.49 | 0.00 | 0.00 | 0.00 | 0.70 | 0.51 | 0.90 |
| Visual hOc4v R | 61 | 69 | 0.38 | -0.02 | 0.27 | 0.08 | 0.47 | 0.00 | 0.00 | 0.00 | 0.73 | 0.53 | 0.92 |
| Visual hOc2 L | 64 | 71 | 0.33 | 0.03 | 0.26 | 0.07 | 0.45 | 0.00 | 0.00 | 0.00 | 0.74 | 0.55 | 0.93 |
| Visual FG1 L | 65 | 63 | 0.31 | 0.06 | 0.24 | 0.07 | 0.42 | 0.00 | 0.00 | 0.00 | 0.76 | 0.58 | 0.93 |
| Visual hOc4v L | 61 | 70 | 0.30 | 0.05 | 0.23 | 0.04 | 0.43 | 0.00 | 0.00 | 0.00 | 0.77 | 0.57 | 0.96 |
| Visual hOc3d R | 64 | 71 | 0.26 | 0.07 | 0.23 | 0.03 | 0.43 | 0.00 | 0.00 | 0.00 | 0.77 | 0.57 | 0.97 |
| IPL PF R | 62 | 72 | 0.25 | 0.07 | 0.23 | 0.01 | 0.45 | 0.00 | 0.00 | 0.00 | 0.77 | 0.55 | 1.00 |
| Cerebellum VIIa crusl Hem L | 60 | 71 | 0.26 | 0.04 | 0.22 | 0.01 | 0.43 | 0.00 | 0.00 | 0.00 | 0.78 | 0.57 | 0.99 |
| SPL 7A R | 60 | 69 | 0.28 | -0.02 | 0.21 | 0.01 | 0.43 | 0.00 | 0.00 | 0.00 | 0.79 | 0.57 | 1.00 |
| <i>Interpersonal distance</i> | | | | | | | | | | | | | |
| Visual hOc3v L | 59 | 69 | 0.29 | 0.08 | 0.26 | 0.04 | 0.47 | 0.00 | 0.00 | 0.00 | 0.74 | 0.53 | 0.96 |

Note: Common (C) and unique (E) environment together with correlation coefficients for monozygotic (MZ r) and dizygotic (DZ r) twins are also tabulated. Columns with MZ- and DZ-pairs show the total number of twin pairs included for each analysis. Abbreviations: L, left hemisphere; R, right hemisphere.

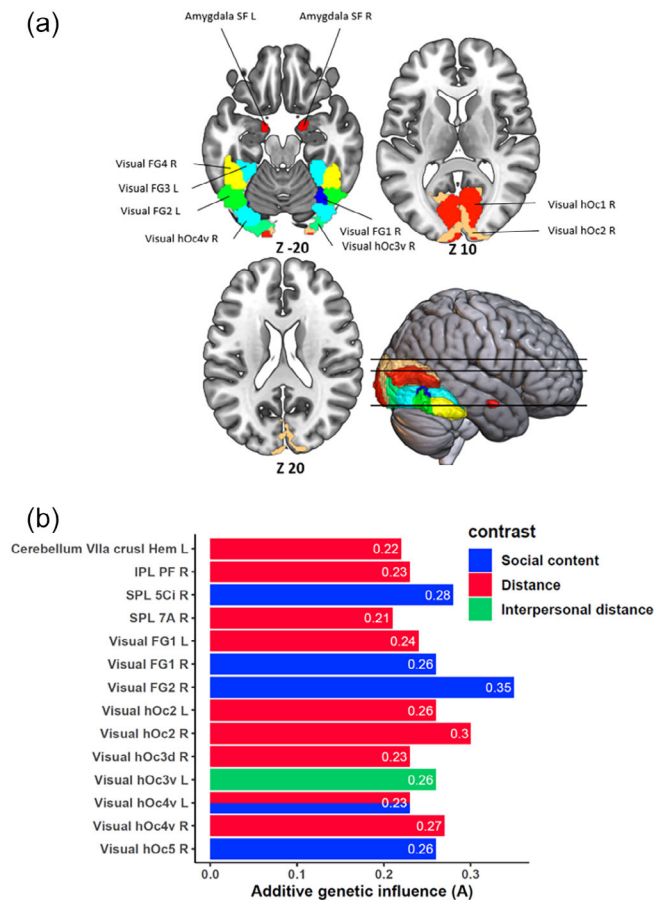


FIGURE 2 Estimated genetic influence on brain function. (a) Locations of ROIs are displayed on an anatomical template brain. (b) Bars show statistically significant (Bonferroni-corrected $p < .05$) additive genetic influence on brain function in regions for social content (blue), distance (red) and interpersonal space (green)

statistically significant ($MZ_n = 59$, $DZ_n = 72$, $A = 0.05$, $n.s.$; $C = 0.00$, $n.s.$). Finally, the genetic influence on the interaction between social content and viewing distance was not statistically significant ($MZ_n = 54$, $DZ_n = 72$, $A = 0.00$, $n.s.$, $C = 0.15$ $n.s.$).

2.12 | Group level fMRI responses

2.12.1 | Neural responses to social content

Across participants, we found greater activation to human figures than cylindrical shapes in the lateral occipital cortex (hOc4lp, hOc4la; Figure 4 for distribution of statistically significant regions) and in an area consistent with the OFA in the inferior occipital gyri (hOc3v, hOc4v; Figure 5). We further noted increased activity in the lateral fusiform gyri in an area consistent with the fusiform face area area (Visual FG2 and FG4). Responses in the amygdala, the hippocampus, basal forebrain, and the visual thalamus were also enhanced by social content (Figure 6). The response in the combined amygdala ROIs was also statistically significant (left amygdala: $t_{293} = 6.24$, $p < .05$, Bonferroni-corrected; right amygdala: $t_{293} = 8.45$, $p < .05$,

Bonferroni-corrected). Continuing to the prefrontal cortex, ventromedial regions, including the subgenual anterior cingulate cortex (BA25), the orbitofrontal cortex (OFC Fo1, Fo3) and the frontal pole (Fp1, Fp2) showed increased responses to social content. Responses were increased also more laterally in inferior frontal cortex (BA44, BA45). Finally, we found increases in the cerebellum (lobuleVIIa crus1) and the inferior parietal lobule (PGa). See Table 2 for statistics.

2.12.2 | Neural responses tracking distance

Next, we compared responses to proximal and distant presentations to determine which ROIs increased their activity to proximal stimuli. There was a significant increased response in medial occipital areas including the calcarine gyrus (hOc1, hOc2) and cuneus (Visual hOc3d and hOc4d), stretching up dorsally to the superior parietal lobule (IPL7a, IPL7m). In the inferior occipital lobe, the ventral parts of V3 and V4 were activated (Visual hOc4v and hOc3v; Figure 5). All areas of the fusiform gyrus (FG1-FG4) were activated, although medial parts showed greater activation than lateral parts. In the medial temporal lobe, we observed significant increase to proximal stimuli in the hippocampus and the amygdala (Figure 6). We also observed a statistically significant response in the combined amygdala ROIs (left amygdala: $t_{293} = 9.59$, $p < .05$, Bonferroni-corrected; right amygdala: $t_{293} = 9.29$, $p < .05$, Bonferroni-corrected). The visual parts of the thalamus and the basal forebrain were also activated. Several areas in the cerebellum showed increased responses as a function of proximal viewing distance. We further found activation in the inferior frontal cortex (Broca 44, 45) and in the orbitofrontal cortex (OFC 3). Table 3 for statistics.

2.12.3 | Neural responses showing an interaction between social content and distance

We observed an interaction between social content and distance in areas of the middle occipital cortex (hOc3v and hOc4v) and in the lateral occipital cortex (hOc4lp) (Figure 5). The regions in the middle occipital cortex were consistent with the OFA and responses were greater to proximal human figures than cylinders. This pattern of responses was observed also in the superficial part of the amygdala (Table 4 and Figure 6). Whereas activation in the OFA was greater to social figures than cylinders both at proximal ($t_{293} = 16.65$, $p < .05$) and distant ($t_{293} = 8.84$, $p < .05$) viewing distances, activation in the superficial part of the amygdala was only facilitated by social content at proximal viewing distance (proximal: $t_{293} = 9.28$, $p < .05$, distant: $t_{293} = 1.45$, $p = 1$). There was no interaction between social content and distance on brain responses for our combined amygdala ROIs.

2.12.4 | Comparison of responses to social content and distance across ROIs

When comparing responses across regions in the occipital cortex (see Table 5 for simplified results summary and Table S2 for t-statistics),

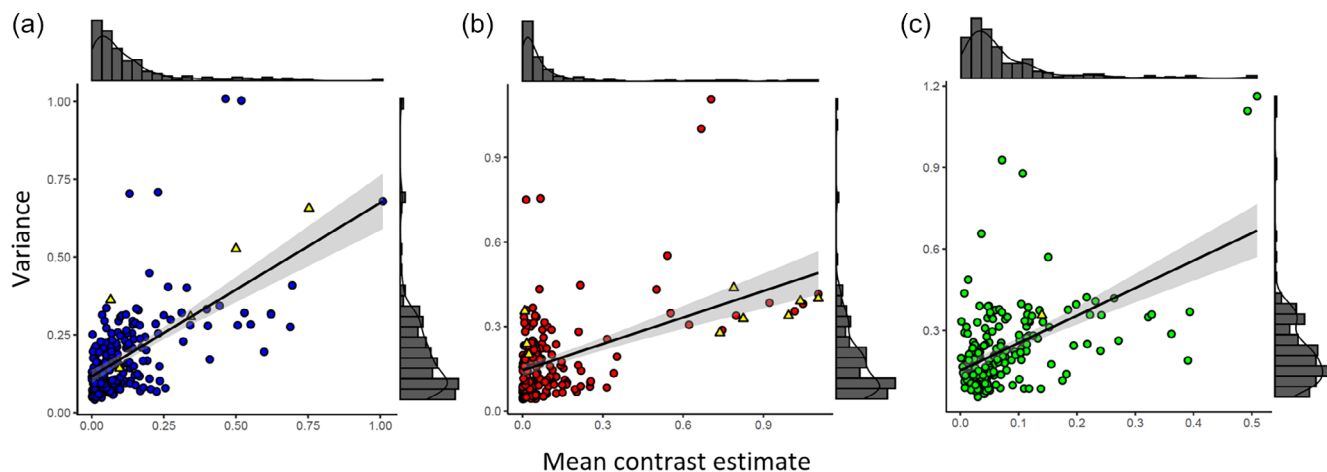


FIGURE 3 Scatter plots of variance and mean contrast estimate. Plots are based on significantly (Bonferroni-corrected $p < .05$) activated brain regions across all contrasts. Variance is calculated using the standard deviation for each brain region included in the analysis. Plots are separated by social content (a), distance (b) and interpersonal distance (c). Yellow triangles denote regions with statistically significant (Bonferroni-corrected $p < .05$) genetic influence on brain activation

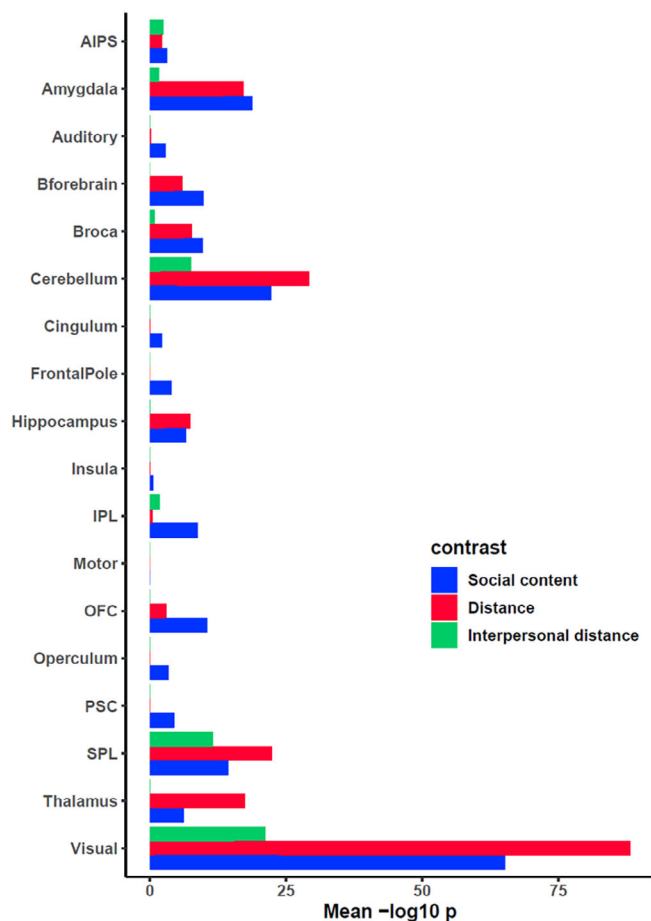


FIGURE 4 Distribution of p values across ROIs. Bars display mean $-\log_{10} p$ values partitioned into brain regions

proximal distance increased responses to a larger extent than social stimuli in V1 and V2 as well as the dorsal parts of V3 and V4. Social stimuli activated the lateral part of V4 (Oc4la, Oc4lp) and V5 to a

larger extent than the distance manipulation, but only in the right hemisphere. In the parietal cortex, the medial and posterior parts of the superior parietal lobule (SPL 7 m, SPL 7p) were more responsive to proximal presentations than to social content, whereas the inferior parietal lobule (IPL PGa) was more activated by social content (Table S2). When we compared responses to social content and distance across brain territories, we found the highest frequency of statistically significant results in the visual regions (Figure 4).

The fusiform face area (FG2, FG4) was activated both by social content and by proximal viewing distance, while the more medial parts of the fusiform gyrus (FG1, FG3) were activated by proximal distance only (Figure 5). There was also an overlap in activation of the ventral portions of visual areas V3 and V4 to the distance manipulation and to social content. However, the lateral parts of V4 (hOc4la, hOc4lp) together with area V5 were activated to a greater degree by social content than proximal distance (Table S2, Figure 5).

In the medial temporal lobe, activations to proximal viewing distance and social content were not significantly different when correcting for multiple comparisons across all ROIs. In the prefrontal cortex, however, the medial orbitofrontal cortex (OFC1) was activated to a greater degree by social content than by the distance manipulation (Table S2).

2.12.5 | Sensitivity analysis

To control for potential confounds based on participants' sex, we compared brain activations for all contrasts (social content, distance, and interpersonal distance) for all ROIs. We found no statistically significant difference between men or women. Hence, results seem to generalize over the sexes.

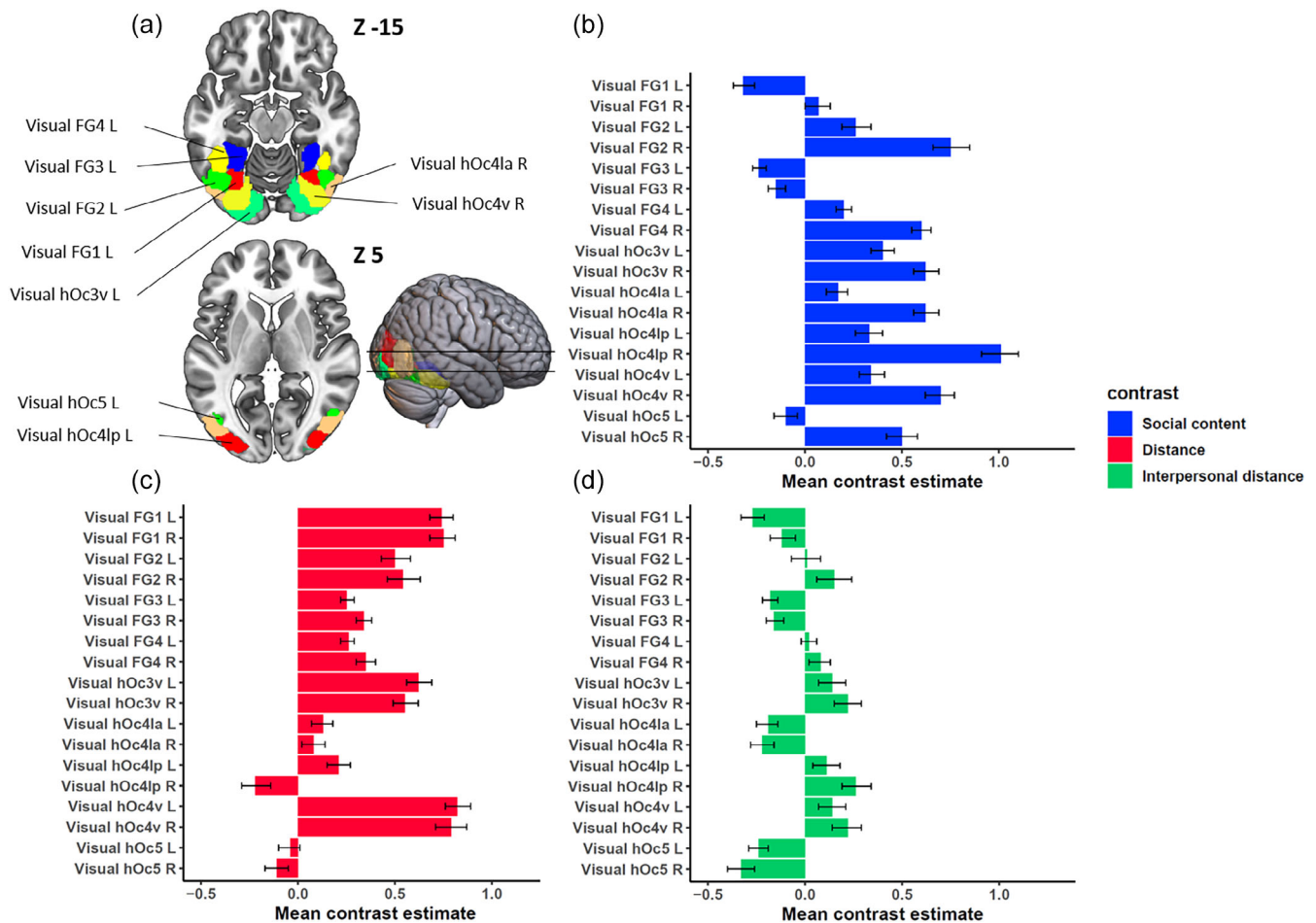


FIGURE 5 Activations of inferior occipital regions and the fusiform gyrus. (a) Locations of ROIs are displayed on an anatomical template brain. (b) Mean contrast estimates for the comparison human figure > cylinder. The lateral parts of the fusiform gyrus (FG2 and FG4), including FFA, show greater estimates than medial parts (FG1 and FG3). (c) Mean contrast estimates for the comparison proximal > distant. Greater contrast estimates were observed in ventral V3 and V4 (hOc3v, hOc4v) together with both medial and lateral parts of fusiform gyrus. The lateral parts of the occipital cortex (hOc4la, hOc4lp, hOc5) were less activated by the distance manipulation than by social content. (d) Mean contrast estimates for the interaction social \times distance, indicative of interpersonal distance monitoring. Greater contrast estimates were observed in ventral V3 and V4 (hOc3v, hOc4v). Error bars represent 95% confidence intervals

2.12.6 | Autonomic responses to interpersonal distance, social content, and distance

We examined the effect of social content and distance on SCR using simple t tests. SCR was facilitated by distance (proximal ($M = 1.18$, $SD = 0.21$) compared to distant ($M = 0.82$, $SD = 0.21$) objects) ($t_{292} = 14.76$, $p < .05$). SCR was, however, similar to social characters ($M = 1.01$, $SD = 0.20$) and nonsocial cylinders ($M = 0.99$, $SD = 0.20$) ($t_{292} = 0.94$, $p = .34$). For the interaction between social content and distance, we calculated the change score by subtracting proximal and distant trials for social characters and nonsocial cylinders separately, and then compared the scores. We found no statistically significant interaction between social content ($M = 0.02$, $SD = 0.40$) and distance ($M = 0.358$, $SD = 0.42$) ($t_{292} = 0.43$, $p = .67$). Comparing the results between men and women using two-sample t -tests, we found no statistically significant main effects [social content: $t_{291} = 1.83$, $p = .07$,

(women: $M = 0.06$, $SD = 0.39$, men: $M = 0.03$, $SD = 0.42$); distance: $t_{291} = 1.23$, $p = .22$, (women: $M = 0.39$, $SD = 0.38$, men: $M = 0.32$, $SD = 0.46$); interpersonal space: $t_{291} = 0.03$, $p = .98$, (women: $M = 0.03$, $SD = 1.07$, men: $M = 0.03$, $SD = 1.08$)].

3 | DISCUSSION

The aims of this study were to identify brain areas monitoring interpersonal distance and estimate genetic influences on neural and autonomic activations (SCR) in a large sample of twins. We found modest genetic influences on brain activations related to social content and distance in the OFA and the fusiform face area as well as in the cerebellum and parietal cortex. The superficial part of the amygdala, the lateral occipital cortex, and the OFA were sensitive to the interaction between social content and distance, consistent with these areas playing a role in monitoring interpersonal distance. A genetic influence

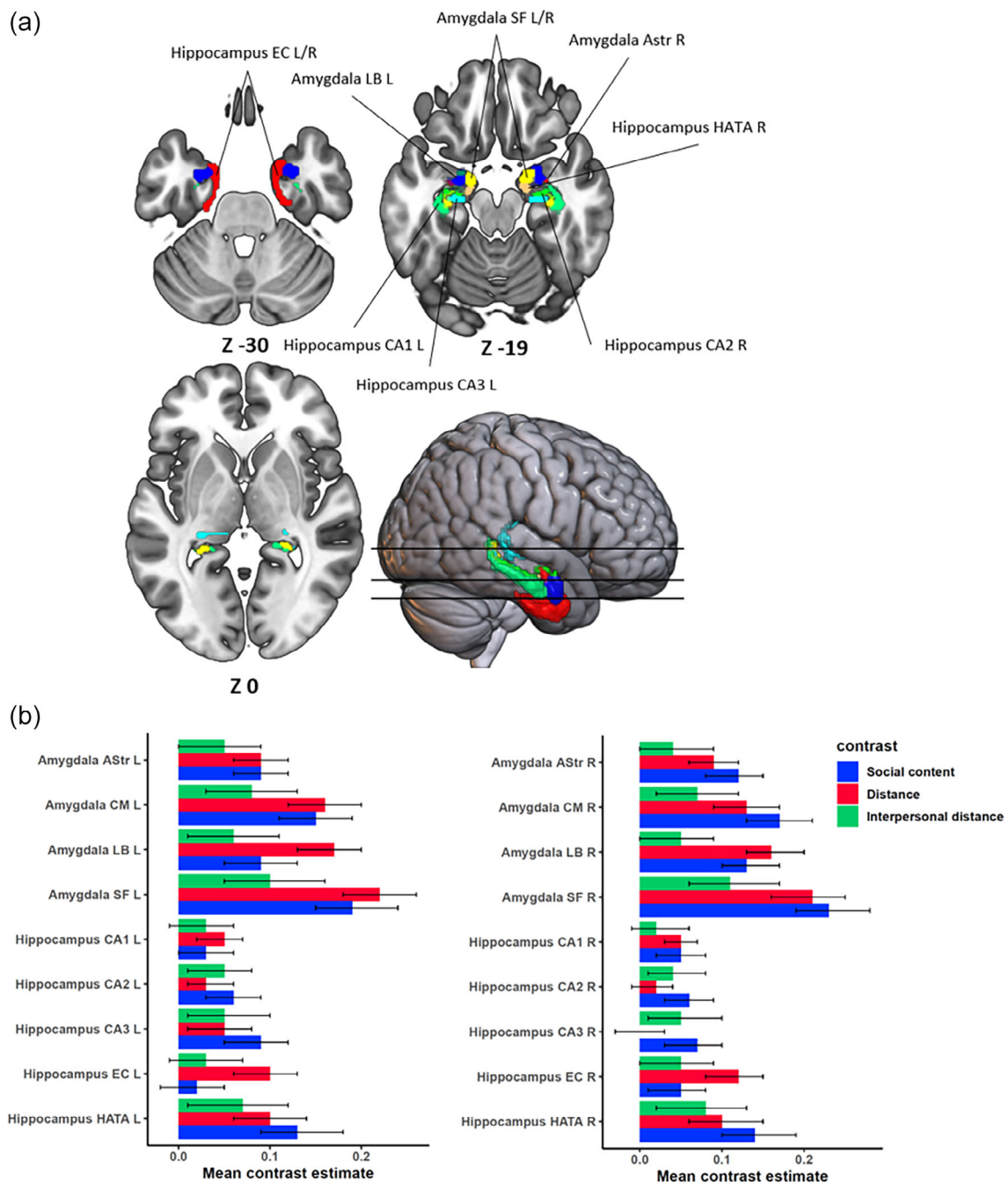


FIGURE 6 Comparison of contrast estimates for social content, distance and interpersonal distance in amygdala and hippocampus. (a) Locations of ROIs are displayed on an anatomical template brain. (b) Bars show mean contrast estimates in the amygdala and hippocampal regions divided by social content (blue), distance (red) and interpersonal distance (green). Error bars represent 95% confidence intervals

on interpersonal space related activation was evident in the OFA, but not the amygdala.

In the occipital and fusiform face area, we found a genetic influence on activation to social content. Responses to faces were previously reported to correlate between MZ twin pairs (Polk et al., 2007a) in the fusiform face area. In a more recent publication, genetic effects on face-related responses were observed in both the occipital and fusiform face areas, as we also found (Abbasi et al., 2020). These additive genetic effects explained around 20% of the variance in face-

related activity, which was similar to the effect that we report here. Further, genetic influence on face-related responses in amygdala were nonsignificant in the study by Abbasi et al. (2020), which could indicate a stronger environmental influence on face perception in this brain region, consistent with the idea that the amygdala is involved in threat learning.

Genetic influences on responses sensitive to proximal viewing distance were found in early visual cortex and the dorsal visual stream including areas of the superior parietal sulcus involved in sensory-

TABLE 2 Brain activation to social content (Bonferroni-corrected $p < .05$)

| Region | t_{293} | $-\log_{10} p$ | Contrast estimate | 95% CI lower | 95% CI upper |
|-----------------------------|-----------|----------------|-------------------|--------------|--------------|
| Visual FG4 R | 23.16 | 65.14 | 0.60 | 0.55 | 0.65 |
| Visual hOc4lp R | 20.99 | 57.30 | 1.01 | 0.91 | 1.10 |
| Visual hOc4la R | 18.95 | 49.81 | 0.62 | 0.56 | 0.69 |
| Visual hOc3v R | 18.88 | 49.56 | 0.62 | 0.56 | 0.69 |
| Visual hOc4v R | 18.63 | 48.64 | 0.70 | 0.62 | 0.77 |
| Visual FG2 R | 15.94 | 38.59 | 0.75 | 0.66 | 0.85 |
| Visual hOc3v L | 13.06 | 27.99 | 0.40 | 0.34 | 0.46 |
| Visual hOc5 R | 11.81 | 23.56 | 0.50 | 0.42 | 0.58 |
| Visual hOc4v L | 10.58 | 19.34 | 0.34 | 0.28 | 0.41 |
| Amygdala SF R | 10.42 | 18.80 | 0.23 | 0.19 | 0.28 |
| Visual FG4 L | 10.38 | 18.68 | 0.20 | 0.16 | 0.24 |
| Visual hOc4lp L | 8.91 | 13.97 | 0.33 | 0.26 | 0.40 |
| Amygdala CM R | 8.30 | 12.12 | 0.17 | 0.13 | 0.21 |
| Amygdala SF L | 8.05 | 11.38 | 0.19 | 0.15 | 0.24 |
| OFC Fo1 L | 7.74 | 10.47 | 0.23 | 0.17 | 0.29 |
| Bforebrain 4 R | 7.50 | 9.83 | 0.13 | 0.10 | 0.17 |
| Broca 45 R | 7.47 | 9.73 | 0.18 | 0.13 | 0.22 |
| Amygdala CM L | 7.36 | 9.43 | 0.15 | 0.11 | 0.19 |
| Amygdala LB R | 7.23 | 9.08 | 0.13 | 0.10 | 0.17 |
| Visual FG2 L | 7.14 | 8.83 | 0.26 | 0.19 | 0.34 |
| Amygdala AStr R | 6.51 | 7.19 | 0.12 | 0.08 | 0.15 |
| OFC Fo1 R | 6.40 | 6.90 | 0.17 | 0.12 | 0.23 |
| Hippocampus HATA R | 6.26 | 6.56 | 0.14 | 0.10 | 0.19 |
| Thalamus Visual R | 6.13 | 6.26 | 0.10 | 0.07 | 0.13 |
| Hippocampus HATA L | 5.99 | 5.92 | 0.13 | 0.09 | 0.18 |
| Bforebrain 4 L | 5.94 | 5.80 | 0.11 | 0.07 | 0.15 |
| Visual hOc4la L | 5.89 | 5.69 | 0.17 | 0.11 | 0.22 |
| Amygdala AStr L | 5.37 | 4.49 | 0.09 | 0.06 | 0.12 |
| Broca 45 L | 5.31 | 4.36 | 0.14 | 0.09 | 0.19 |
| OFC Fo3 R | 5.20 | 4.13 | 0.11 | 0.07 | 0.15 |
| FrontalPole Fp2 L | 5.11 | 3.95 | 0.20 | 0.12 | 0.28 |
| Amygdala LB L | 4.93 | 3.56 | 0.09 | 0.05 | 0.13 |
| FrontalPole Fp2 R | 4.84 | 3.38 | 0.16 | 0.10 | 0.23 |
| IPL PGa L | 4.69 | 3.08 | 0.16 | 0.09 | 0.23 |
| Hippocampus CA3 L | 4.66 | 3.03 | 0.09 | 0.05 | 0.12 |
| FrontalPole Fp1 L | 4.49 | 2.68 | 0.14 | 0.08 | 0.20 |
| Cingulum 25 L | 4.25 | 2.24 | 0.08 | 0.04 | 0.12 |
| Hippocampus CA2 R | 4.20 | 2.15 | 0.06 | 0.03 | 0.09 |
| Hippocampus CA2 L | 4.06 | 1.90 | 0.06 | 0.03 | 0.09 |
| FrontalPole Fp1 R | 4.00 | 1.79 | 0.12 | 0.06 | 0.18 |
| Cingulum 25 R | 3.85 | 1.54 | 0.07 | 0.04 | 0.11 |
| Cerebellum VIIa crus1 Hem L | 3.76 | 1.39 | 0.10 | 0.05 | 0.15 |

Abbreviations: L, left hemisphere; R, right hemisphere.

motor integration. Distance-related responses in the OFA and the medial part of the fusiform gyrus were also genetically influenced. Hence, in the OFA, we observed a genetic influence both on

responses to proximal distance and social content. In this brain region, we also found a genetic influence on activity tracking interpersonal distance. The genetic influence on activations in the OFA is in line

TABLE 3 Brain activation to distance (Bonferroni-corrected $p < .05$)

| Region | t_{293} | $-\log_{10} p$ | Contrast estimate | 95% CI lower | 95% CI upper |
|-----------------------------|-----------|----------------|-------------------|--------------|--------------|
| Visual hOc3d R | 29.96 | 88.19 | 1.11 | 1.03 | 1.18 |
| Visual hOc1 L | 29.40 | 86.39 | 1.11 | 1.03 | 1.18 |
| Visual hOc3d L | 29.30 | 86.04 | 1.05 | 0.95 | 1.09 |
| Visual hOc2 L | 29.29 | 86.00 | 1.04 | 0.93 | 1.06 |
| Visual hOc1 R | 29.14 | 85.52 | 1.02 | 0.98 | 1.12 |
| Visual hOc2 R | 28.49 | 83.41 | 0.99 | 0.97 | 1.11 |
| Visual hOc4d R | 25.52 | 73.40 | 0.92 | 0.85 | 0.99 |
| Visual hOc4v L | 24.71 | 70.59 | 0.82 | 0.76 | 0.89 |
| Visual FG1 L | 24.00 | 68.13 | 0.80 | 0.68 | 0.80 |
| Visual FG1 R | 23.87 | 67.66 | 0.79 | 0.68 | 0.81 |
| Visual hOc4d L | 23.51 | 66.40 | 0.75 | 0.73 | 0.86 |
| Visual hOc4v R | 20.48 | 55.45 | 0.74 | 0.71 | 0.87 |
| Visual hOc3v L | 19.29 | 51.06 | 0.70 | 0.56 | 0.69 |
| Visual hOc3v R | 16.09 | 39.17 | 0.67 | 0.49 | 0.62 |
| Visual FG3 R | 15.97 | 38.70 | 0.62 | 0.30 | 0.38 |
| Visual FG4 R | 13.76 | 30.56 | 0.55 | 0.30 | 0.40 |
| Visual FG3 L | 13.53 | 29.72 | 0.54 | 0.22 | 0.29 |
| Visual FG4 L | 13.46 | 29.46 | 0.50 | 0.22 | 0.29 |
| Cerebellum VI Hem L | 13.38 | 29.17 | 0.35 | 0.27 | 0.36 |
| Visual FG2 L | 13.07 | 28.04 | 0.34 | 0.43 | 0.58 |
| Visual FG2 R | 12.50 | 25.99 | 0.32 | 0.46 | 0.63 |
| Cerebellum VI Hem R | 11.68 | 23.11 | 0.31 | 0.21 | 0.29 |
| SPL 7 M L | 11.48 | 22.42 | 0.26 | 0.58 | 0.83 |
| SPL 7 M R | 11.44 | 22.28 | 0.25 | 0.55 | 0.78 |
| Thalamus Visual R | 9.98 | 17.38 | 0.25 | 0.12 | 0.18 |
| Amygdala SF L | 9.91 | 17.12 | 0.22 | 0.18 | 0.26 |
| Amygdala LB R | 9.18 | 14.79 | 0.22 | 0.13 | 0.20 |
| Amygdala LB L | 8.97 | 14.14 | 0.21 | 0.13 | 0.20 |
| Amygdala SF R | 8.84 | 13.76 | 0.21 | 0.16 | 0.25 |
| Amygdala CM L | 8.13 | 11.61 | 0.20 | 0.12 | 0.20 |
| Cerebellum VIIa crusl Hem L | 7.63 | 10.18 | 0.20 | 0.16 | 0.27 |
| Visual hOc4lp L | 6.77 | 7.86 | 0.17 | 0.15 | 0.27 |
| Broca 45 L | 6.71 | 7.71 | 0.16 | 0.11 | 0.20 |
| Hippocampus EC R | 6.58 | 7.38 | 0.16 | 0.08 | 0.15 |
| Cerebellum V Hem L | 6.37 | 6.85 | 0.15 | 0.09 | 0.16 |
| SPL 7P L | 6.26 | 6.56 | 0.15 | 0.22 | 0.42 |
| Amygdala AStr L | 6.24 | 6.53 | 0.15 | 0.06 | 0.12 |
| Cerebellum VI Verm L | 6.21 | 6.45 | 0.14 | 0.14 | 0.27 |
| Amygdala CM R | 6.20 | 6.41 | 0.13 | 0.09 | 0.17 |
| Cerebellum VI Verm R | 6.13 | 6.26 | 0.13 | 0.13 | 0.26 |
| Amygdala AStr R | 6.08 | 6.13 | 0.13 | 0.06 | 0.12 |
| Broca 45 R | 6.07 | 6.11 | 0.12 | 0.10 | 0.19 |
| Bforebrain 4 L | 6.03 | 6.00 | 0.11 | 0.08 | 0.15 |
| Thalamus Visual L | 5.85 | 5.58 | 0.11 | 0.05 | 0.10 |
| Hippocampus EC L | 5.58 | 4.96 | 0.10 | 0.06 | 0.13 |
| Cerebellum VIIa crusl Hem R | 5.39 | 4.54 | 0.10 | 0.09 | 0.20 |

TABLE 3 (Continued)

| Region | t_{293} | $-\log_{10} p$ | Contrast estimate | 95% CI lower | 95% CI upper |
|--------------------|-----------|----------------|-------------------|--------------|--------------|
| Bforebrain 4 R | 5.27 | 4.29 | 0.10 | 0.06 | 0.13 |
| Hippocampus HATA L | 5.07 | 3.85 | 0.10 | 0.06 | 0.14 |
| Broca 44 L | 5.04 | 3.80 | 0.09 | 0.07 | 0.16 |
| Cerebellum V Hem R | 4.88 | 3.45 | 0.09 | 0.05 | 0.12 |
| OFC Fo3 L | 4.64 | 2.98 | 0.09 | 0.05 | 0.13 |
| OFC Fo3 R | 4.49 | 2.70 | 0.09 | 0.05 | 0.12 |
| Hippocampus HATA R | 4.42 | 2.57 | 0.08 | 0.06 | 0.15 |
| Visual hOc4la L | 4.41 | 2.55 | 0.08 | 0.07 | 0.18 |
| Hippocampus CA1 R | 4.05 | 1.88 | 0.05 | 0.03 | 0.07 |
| Hippocampus CA1 L | 3.73 | 1.34 | 0.05 | 0.02 | 0.07 |

Abbreviations: L, left hemisphere; R, right hemisphere.

TABLE 4 Brain activation to interpersonal distance (Bonferroni-corrected $p < .05$)

| Region | t_{293} | $-\log_{10} p$ | Contrast estimate | 95% CI lower | 95% CI upper |
|-----------------|-----------|----------------|-------------------|--------------|--------------|
| Visual hOc4lp R | 6.99 | 8.44 | 0.26 | 0.19 | 0.34 |
| Visual hOc3v R | 6.37 | 6.84 | 0.22 | 0.15 | 0.29 |
| Visual hOc4v R | 5.72 | 5.28 | 0.22 | 0.14 | 0.29 |
| Visual hOc3v L | 4.02 | 1.83 | 0.14 | 0.07 | 0.21 |
| Amygdala SF R | 3.91 | 1.65 | 0.11 | 0.06 | 0.17 |
| Amygdala SF L | 3.84 | 1.52 | 0.10 | 0.05 | 0.16 |
| Visual hOc4v L | 3.81 | 1.47 | 0.14 | 0.07 | 0.21 |

Abbreviations: L, left hemisphere; R, right hemisphere.

with findings suggesting that brain activity to social agents in this region is present already in young infants (Deen et al., 2017). Our findings suggest that information about distance to social stimuli may be integrated in the processing of social stimuli in this region and support that this type of processing is innate.

Responses in the OFA (hOc3v, hOc4v) were greater to human figures than cylinders as a function of viewing distance, indicating that this region could play a role in monitoring interpersonal distance. The OFA has been suggested to be the first node in a face perception network where social features are represented before processing of increasingly complex facial features in higher face-processing regions (Kragel et al., 2019). Our finding suggest that interpersonal distance may be represented at this early processing stage in the face network.

The right lateral occipital cortex (hOc4lp) was the area with the greatest increase in response to proximal human figures as compared to cylindrical shapes. This region has previously been implicated in processing of social stimuli as well as objects (Grill-Spector et al., 2017), and it has a preference for visual shapes at least from 6 months of age (Emberson et al., 2017). The lateral occipital cortex receives major projections from the dorsal visual stream via the vertical occipital fasciculus (Jitsuishi et al., 2020). The vertical occipital fasciculus has been linked to stereoscopic vision, which is important for depth perception necessary for determining interpersonal distance (Palejwala et al., 2020). Also, the joint connectivity of the lateral occipital cortex to the dorsal and ventral visual stream, may be a reason for

the involvement of this area in interpersonal distance monitoring. The lateral occipital cortex is also connected to the medial temporal lobe via the inferior longitudinal fasciculus (Latini et al., 2017; Palejwala et al., 2020), and could interact with amygdala and the hippocampus. Interestingly, responses in the lateral occipital cortex only changed as a function of viewing distance to proximal human figures, but not to cylindrical shapes. This suggests that the positions of human figures could be decoded in this area to a larger extent than the position of geometrical shapes. Supporting the idea that human positions are decoded here, this area has been reported to be sensitive to socially meaningful positions, such as whether figures are standing face to face or facing away from each other (Papeo, 2020). The lateral occipital cortex also has long range white matter connections with the frontal pole (Orr et al., 2015). Information about social content in visual images could be transmitted to the medial prefrontal cortex via this pathway, which could explain activations observed in the frontal pole and orbitofrontal cortex for social content in our study.

In the amygdala, which is considered an extended part of the face network, all three subparts that were investigated were activated bilaterally by both social content and viewing distance. The only area of the amygdala where proximal viewing distance had greater effect on responses to human figures than cylindrical shapes was the superficial part, suggesting a role for this region in monitoring interpersonal distance. Although this finding needs to be interpreted with caution given our relatively large voxel and smoothing kernel size. The finding

| Left hemisphere | S | D | I | Right hemisphere | S | D | I |
|-----------------------------|---|---|---|-----------------------------|---|---|---|
| Amygdala AStr L | * | * | | Amygdala AStr R | * | * | |
| Amygdala CM L | * | * | | Amygdala CM R | * | * | |
| Amygdala LB L | * | * | | Amygdala LB R | * | * | |
| Amygdala SF L | * | * | * | Amygdala SF R | * | * | * |
| Bforebrain 4 L | * | * | | Bforebrain 4 R | * | * | |
| Broca 44 L | | * | | Broca 45 R | * | * | |
| Broca 45 L | * | * | | Cerebellum V Hem R | | * | |
| Cerebellum V Hem L | | * | | Cerebellum VI Hem R | | * | |
| Cerebellum VI Hem L | | * | | Cerebellum VI Verm R | | * | |
| Cerebellum VI Verm L | | * | | Cerebellum VIIa crusI Hem R | | * | |
| Cerebellum VIIa crusI Hem L | * | * | | Cingulum 25 R | * | | |
| Cingulum 25 L | * | | | FrontalPole Fp1 R | * | | |
| FrontalPole Fp1 L | * | | | FrontalPole Fp2 R | * | | |
| FrontalPole Fp2 L | * | | | Hippocampus CA1 R | | | * |
| Hippocampus CA1 L | | * | | Hippocampus CA2 R | * | | |
| Hippocampus CA2 L | * | | | Hippocampus EC R | | | * |
| Hippocampus CA3 L | * | | | Hippocampus HATA R | * | * | |
| Hippocampus EC L | | * | | OFC Fo1 R | * | | |
| Hippocampus HATA L | * | * | | OFC Fo3 R | * | * | |
| IPL PGa L | * | | | SPL 7M R | | | * |
| OFC Fo1 L | * | | | Thalamus Visual R | * | * | |
| OFC Fo3 L | | * | | Visual FG1 R | | | * |
| SPL 7M L | | * | | Visual FG2 R | * | * | |
| SPL 7P L | | * | | Visual FG3 R | | | * |
| Thalamus Visual L | | * | | Visual FG4 R | * | * | |
| Visual FG1 L | | * | | Visual hOc1 R | | | * |
| Visual FG2 L | * | * | | Visual hOc2 R | | | * |
| Visual FG3 L | | * | | Visual hOc3d R | | | * |
| Visual FG4 L | * | * | | Visual hOc3v R | * | * | * |
| Visual hOc1 L | | * | | Visual hOc4d R | | | * |
| Visual hOc2 L | | * | | Visual hOc4la R | * | | |
| Visual hOc3d L | | * | | Visual hOc4lp R | * | | * |
| Visual hOc3v L | * | * | * | Visual hOc4v R | * | * | * |
| Visual hOc4d L | | * | | Visual hOc5 R | * | | |
| Visual hOc4la L | * | * | | | | | |
| Visual hOc4lp L | * | * | | | | | |
| Visual hOc4v L | * | * | * | | | | |

TABLE 5 Comparison of activated brain regions between contrasts. Social content (S), distance (D) and interpersonal distance (I) are tabulated separately, and statistically significant activation is marked with a star

that the amygdala is important for judgment of interpersonal distance mirrors findings from patients with selective amygdala damage (Kennedy et al., 2009) also commensurates with neuroimaging studies (Buades-Rotger et al., 2017). However, these studies have not parcellated the amygdala into subparts as we did here. Using this division of the amygdala revealed that the superficial part is more involved in interpersonal distance than centromedial and basolateral parts. One reason for this could be that the different subparts of the amygdala have different connectivity, as previously reported (Roy et al., 2020). A more recent publication compared the connectivity of

the same three subdivisions of the amygdala we used in the present study (Sylvester et al., 2020). While the centromedial part showed stronger connectivity to the default mode network, the superficial part was more strongly connected with the dorsal attention network. The increased connectivity with the dorsal attention network could partially be a reason for the superficial subdivision of the amygdala being more strongly associated with interpersonal space manipulations in our study.

The amygdala is known to be central for the acquisition of conditioned fear (LeDoux, 2000). When conditioned fear is acquired to

cues presented at near or far distance, the connectivity pattern of the amygdala changes depending on viewing distance (Faul et al., 2020). This suggests that the amygdala is sensitive to distance manipulations during fear conditioning. Fear conditioning can also change the preferred interpersonal distance to cues that have been learned to be threatening (Ahs et al., 2015). This could imply that amygdala-dependent plasticity is important for flexibly adapting interpersonal distance based on previous experience. The increased amygdala activation that we observed to our interpersonal distance manipulation could form the basis for such amygdala dependent learning.

A region that has received little attention in the literature on interpersonal distance is the hippocampus. Subfields CA2 and CA3 of the hippocampus have been shown to play a role in social memory in mice (Hitti & Siegelbaum, 2014), in particular CA (Chiang et al., 2018). In our study, activation to social stimuli in the hippocampus were relatively large in subfields CA2 and CA3, which might indicate that CA2 and CA3 are tuned to social information in humans as they are in mice. Responses in the entorhinal cortex and subfield CA1, on the other hand, were more related to the distance manipulation. This finding is also in line with research in mice showing that grid cells and place cells are found in these areas (Gil et al., 2018). Although we did not observe an interaction between distance and social content in the hippocampus, the dissociation between subfields of the hippocampus in their preference for social content and viewing distance could play a role for how memories such events are represented.

One limitation with our experimental setup is that we did not control for effects of agency. Agency or action potential of animate and inanimate objects has been suggested to regulate interpersonal space boundaries (Lloyd, 2009). We compared responses to humanoid characters with cylindrical objects, and it is possible that a comparison with an animal, would have yielded different results for the distance manipulation. Another potential limitation with our experiment manipulation is that we did not control for the size of objects with our distance manipulation. Although our present experiment did not contain a critical control for size, we have previously shown that smaller-sized characters can elicit greater SCR than larger-sized spheres (Rosén et al., 2017, 2019). Our previous results therefore indicated that type of stimuli, and not size, affected the autonomic response to proximal objects. However, we also want to emphasize that size is a determinant of defensive behaviors, as has been shown in studies of looming, where a circle expanding in size elicits escape responses (Yilmaz & Meister, 2013). Hence, even if we cannot fully disentangle the effect of distance and size in our study, both are likely important for brain responses related to changes in distance. Another possible concern is that we did not design the experiment to compare differences in brain responses to the two different male characters. The trials were balanced for social content and distance but not on individual stimulus features (type of humanoid character or color of cylinder).

4 | CONCLUSION

In conclusion, we report genetic effects on brain function relevant to monitoring of interpersonal distance in the OFA. We also found that

activation of the superficial part of the amygdala was related to interpersonal distance, although the genetic influence in this region was negligible. Findings suggest that environmental influences on neural processes regulating interpersonal distance may act at the level of the amygdala, whereas genetic effects predominantly influence function in lateral occipital regions.

ACKNOWLEDGMENTS

This research was supported by grants from the Swedish Research Council (2014-01160; 2018-01322) and Bank of Sweden Tercentenary Foundation (P20-0125).

CONFLICT OF INTEREST

Henrik Larsson has served as a speaker for EvolanPharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. All other authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Jörgen Rosén and Fredrik Åhs: Designed the experiment; original draft (lead). Granit Kastrati and Jörgen Rosén: Performed the experiments. Jörgen Rosén and Ralf Kuja-Halkola: Analyzed the data, and Jörgen Rosén Ralf Kuja-Halkola, Henrik Larsson, and Fredrik Åhs: Contributed to interpretation of results. All authors substantially read, revised the manuscript, and approved the manuscript.

DATA AVAILABILITY STATEMENT

All data generated during the current study can be made available upon reasonable request from the corresponding author.

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How to cite this article: Rosén, J., Kastrati, G., Kuja-Halkola, R., Larsson, H., & Åhs, F. (2022). A neuroimaging study of interpersonal distance in identical and fraternal twins. *Human Brain Mapping*, 43(11), 3508–3523. <https://doi.org/10.1002/hbm.25864>