Brain volumetric changes in the general population following the COVID-19 outbreak and lockdown

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) outbreak introduced unprecedented health-risks, as well as pressure on the economy, society, and psychological well-being due to the response to the outbreak. In a preregistered study, we hypothesized that the intense experience of the outbreak potentially induced stress-related brain modifications in the healthy population, not infected with the virus. We examined volumetric changes in 50 participants who underwent MRI scans before and after the COVID-19 outbreak and lockdown in Israel. Their scans were compared with those of 50 control participants who were scanned twice prior to the pandemic. Following COVID-19 outbreak and lockdown, the test group participants uniquely showed volumetric increases in bilateral amygdalae, putamen, and the anterior temporal cortices. Changes in the amygdalae diminished as time elapsed from lockdown relief, suggesting that the intense experience associated with the pandemic induced transient volumetric changes in brain regions commonly associated with stress and anxiety. The current work utilizes a rare opportunity for real-life natural experiment, showing evidence for brain plasticity following the COVID-19 global pandemic. These findings have broad implications, relevant both for the scientific community as well as the general public.

1. Introduction

During 2020, the world has been coping with the outbreak of the coronavirus disease 2019 (COVID-19) pandemic that infected millions and resulted in devastating numbers of deaths globally. As an initial response to the first wave of the outbreak, countries closed their borders and implemented a series of ad-hoc laws and orders to restrict the spread of the disease. Countries with major outbreaks such as China, Italy, and Spain enforced stringent restriction of movement for a limited period, referred to here as 'lockdown'. Although lockdowns along with other social distancing restrictions contributed to control the health risks of the outbreak (Vinceti et al., 2020), they also had a negative impact on the social, financial and mental well-being of the general population (Han, 2020; Park et al., 2020), leading to one of the sharpest declines in economic growth over the past decades (Fernandes, 2020; Zhang et al., 2020; Cutler and Summers, 2020). Considering the intense impact of social isolation on psychological well-being (Brooks et al., 2020), it is not surprising that COVID-19 outbreak also led to increased rates of stress and anxiety. These were often even more prevalent in healthy

young adults, suggesting that the high rate psychological distress was attributed to implications beyond actual health risk, such as the difficulties of social isolation and financial insecurity due to the response to the health crisis (Taylor et al., 2020, Salari et al., 2020, Huang and Zhao, 2020). It is now evident that the indirect consequences of the pandemic affected a much larger proportion of the population, having an impact of no lesser gravity than the actual health risks that were meant to be prevented (Park et al., 2020; Gruber, 2020; Qiu et al., 2020).

In Israel, a strict lockdown period was issued from mid-March until the end of April 2020. During its peak, most unessential businesses were closed and civilians' movement for non-essential destinations was restricted to a radius of 100 meters from their homes. Prior to COVID-19, the country had experienced a period of peak economic prosperity (Bank of Israel Research Department 2020), which was interrupted by the outbreak, leading to unprecedented unemployment rates (reaching nearly 30% of the work-force in April 2020) and the collapse of several sectors such as aviation, tourism, and culture (Bank of Israel Research Department 2020b; Bank of Israel Research Department 2020a). The outbreak period was characterized with acute uncertainty and increase

in anxiety, regarding both the health and socioeconomic effects of the pandemic (Tzur Bitan et al., 2020).

In light of the comprehensive effects of COVID-19 outbreak and following lockdown, we hypothesized that the intense experience might be manifested as structural changes in the brain. Over the past years, several studies demonstrated that exogenous experiences and intentional laboratory interventions, such as learning a new skill or gaining expertise in a profession, induced brain plasticity, detectable using T1-weighted magnetic resonance imaging (MRI) (Maguire et al., 2000; Jung et al., 2013; Draganski et al., 2004). However, these works mainly focused on comparing unique groups of experts to non-experts or examined brain changes after some intentional training intervention. To this day, none has been able to track in a longitudinal study a real-world event that induced consistent structural brain changes in the general population.

The current work was initiated as a reaction to the outbreak of COVID-19 in Israel, aiming to study the structural brain plasticity in the general population following a real-life event. For this purpose, we examined $n = 50$ test group participants that were scanned with T1-weighted MRI prior to the outbreak and returned for a follow-up scan at the end of the first nation-wide COVID-19 lockdown period, which was installed from late March to early May 2020 (see methods for a detailed timeline of post COVID-19 follow-up scans). The structural changes of the study group (before versus after the outbreak and lockdown) were compared to those of $n = 50$ control participants who were scanned twice before the COVID-19 outbreak. All participants were healthy, without a history of neurological or psychiatric disorders, did not show COVID-19 symptoms, and were not diagnosed carrying the virus (see the methods section for further demographic information). The unique circumstances imposed due to the COVID-19 lockdown created rare settings for a natural experiment to examine the effect of a real-world intense event on brain plasticity.

Previous neuroimaging studies have commonly linked stress and anxiety processing with the amygdala, both when examining structural differences (Ganzel et al., 2008; Hölzel, 2009; Rogers et al., 2009; Schienle et al., 2011) and functional reactivity (Mochcovitch et al., 2014; Bryant, 2008; Stevens et al., 2017); however structural differences in amygdala often showed inconclusive change patterns, with some studies showing stress was associated with volumetric increase, while others showing a decrease in volume (O'Doherty et al., 2015; Duval et al., 2015; Kennis et al., 2020). Prior to data collection of the full sample, we ran a preliminary pilot study using the same study design with $N = 16$ participants; $n = 8$ participants were scanned after lockdown restrictions were lifted and $n = 8$ participants were randomly sampled from the data pool used to define the control group. The data of these 16 participants were used for a power analysis to determine the minimal sample size for the full study and were not included in the main analyses. In this pilot study we observed prominent volumetric increase in the Amygdalae. Thus, we hypothesized and preregistered that the epicenter for volumetric changes in the current study would be in the Amygdalae. The preregistered hypotheses and general design are available along with the data and analysis codes online (project page: https://osf.io/wu37z/; preregistration: https://osf.io/k6xhn/).

2. Results

Fifty participants who were scanned prior to COVID-19 outbreak, agreed to be scanned again after the relief of COVID-19 lockdown limitation, which were imposed between late March to early May 2020 in Israel (see methods for detailed timeline of COVID-19 outbreak and data collection in the current study). Prior to their follow-up MRI scan session, we asked participants of the post-lockdown test group to fill in a short questionnaire regarding their experience during the lockdown period. Of the participants who agreed to reply, 79.6% reported they did not leave their home for non-essential needs, 57.1% met no more than 3 people (including people living with them in the same house-

hold), 44.9% did not meet their parents at all (avoided all meeting, including with masks or other safety precautions), 38.8% indicated an increased feeling of anxiety following the lockdown, 34.7% anticipated that their future behavior will change after the lockdown, 46.8% reported they were concerned about their personal future well-being, and 42.9% indicated that their employment status was reduced to part-time job, unemployment or furlough. In an exploratory factor analysis (EFA; using Varimax rotation, see methods), we examined which main themes dominated participants' reported experience during the lockdown, and identified two main factors, explaining together 54.0% of the variance in participants' responses. The first factor was highly loaded with questionnaire items that described increased social isolation, while the second was mainly related to increased feelings of anxiety (Fig. 1).

T1-weighted anatomical MRI scans were used as input for deformation and surface-based morphometry (SBM) analysis using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/, University of Jena) for SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/, Wellcome Trust Centre for Neuroimaging). The brain was segmented to 58 regions based on the cortical and subcortical nuclei classifications of the Hammers atlas (Hammers, 2003). Following surface reconstruction, each participant's individual gray matter volume was estimated for each of the 58 anatomically defined regions of interest (ROIs). This procedure accounted for the longitudinal nature of the data, performing the analysis on both scans simultaneously. To avoid voxel-based multiple comparisons, we performed a region-based analysis (following surface projection to the Hammers atlas) and corrected for multiple comparisons using the Benjamini-Hochberg correction (Benjamini and Hochberg, 1995) to control for false discovery rate (FDR; $p_{adj.} < 0.05$). Validation of the pipeline was performed using simulated data and by comparing the results with other software (see methods).

Using linear regression models, we examined volumetric changes, testing for regions with stronger changes for the test group compared to the control group. Examining the interaction effect of session (baseline versus follow-up scans) and experimental group (test versus control) revealed ten anatomical brain regions (composed of bilateral five unique regions in both hemispheres) in which volumetric increases were observed uniquely for the test group (Table 1 and Fig. 2). Most prominently, as we expected and pre-registered, we found a robust volumetric increase effect in the bilateral amygdalae of the test group. We also observed a significant increase in volume bilaterally in the putamen, and in three anatomical regions within the ventral anterior temporal cortex adjacent to each other, namely in the medial part of the anterior temporal lobe, the fusiform gyrus, and the parahippocampal gyrus. We did not observe regions with a significant interaction effect in the opposite direction (i.e., ROIs in which the test group showed relative volumetric decrease compared to the control group).

To examine the spatial distribution within significant ROIs and have better visualization of the results, we performed an additional post-hoc VBM analysis (Fig. 2a). Examining the post-hoc voxel-based results revealed that volumetric changes occurred throughout the entire surface of bilateral amygdalae, while in the putamen the effects occurred mainly in the dorsal area. In the ventral anterior temporal cortices, large connected clusters of volumetric change spanned throughout the three adjacent temporal ROIs, thus suggesting that the three ROIs shared a similar origin. To ensure that the reported effects originated from volumetric changes in the test group following the COVID-19 outbreak and its related lockdown period, we tested for ROIs where the significant interaction effect was accompanied by a significant effect for the test group but not for the control group, and was consistent beyond baseline scans effect or measurement protocol (see methods and supplementary materials).

To evaluate and control for the effect of time between scans and time from lockdown, we included in the model two additional covariates - the time between scans (TBS; which was generally longer for the test group) and time following lockdown (TFL; calculated only for the test group, see methods for more details). The two covariates were not correlated
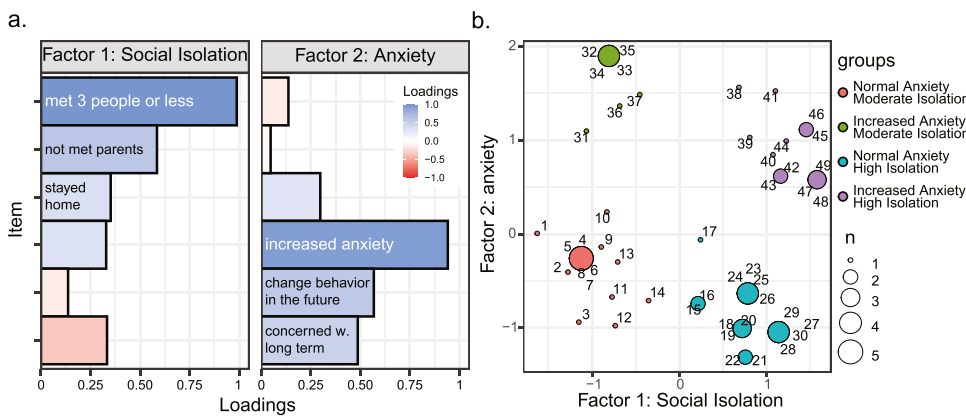
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a.

b.

Fig. 1. Exploratory factor analysis (EFA) of COVID-19 questionnaire.

Exploratory factor analysis of the responses to the questionnaire revealed two main themes characterized the participants. **(a)** The first factor ('Social isolation') strongly related to the item indicating meeting no more than 3 people, as well as to other two related items of avoiding meeting parents and staying at home during lockdown. An increased feeling of anxiety dominated the second factor, along with changing future behavior and concerns regarding the long-term effects. X-axis represents the loading in absolute values of each item with each of the two factors identified in the EFA (color represents loading directionality-positive loading in blue, negative loading in red). **(b)** Dispersion of the 49 participants who responded to the questionnaire, across the two factors. Responders were categorized into binary anxiety (responded they felt an increase in anxiety during lockdown) and isolation groups (reported avoiding meeting their parents or more than three people; represented by different colors). Points represent unique scores; axes represent loading scores on the two EFA factors; frequency is represented by point size and the number of participants' indices around their corresponding data points (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 1

Surface based morphology analysis results

Region	Hemi-sphere	Interaction estimate (95% CI)	Interaction p(FDR adj.)	Test group×session estimate (95% CI) [a]	Test group×session p(FDR adj.)	Change from baseline M (SE) [b] Test (%)	Control (%)
Amygdala	Left	0.09 [0.05, 0.13]	2.4E^{-5} (0.001)	0.08 [0.05, 0.11]	9.8E^{-6} (2.1E^{-4})	4.92 (1.06)	-0.56 (0.6)
	Right	0.08 [0.03, 0.13]	0.003 (0.030)	0.08 [0.05, 0.11]	1.6E^{-5} (2.3E^{-4})	4.47 (1.07)	0.07 (0.86)
Putamen	Left	0.19 [0.09, 0.29]	4.1E^{-4} (0.006)	0.13 [0.06, 0.2]	4.0E^{-4} (0.002)	3.31 (0.83)	-0.5 (0.7)
	Right	0.17 [0.08, 0.26]	2.4E^{-4} (0.005)	0.14 [0.08, 0.2]	1.1E^{-5} (2.1E^{-4})	3.31 (0.67)	-0.01 (0.68)
Anterior temporal lobe (medial part)	Left	0.25 [0.12, 0.38]	1.8E^{-4} (0.005)	0.15 [0.07, 0.23]	4.7E^{-4} (0.003)	2.82 (0.75)	-0.7 (0.76)
	Right	0.21 [0.07, 0.35]	0.004 (0.030)	0.15 [0.05, 0.25]	0.004 (0.023)	2.93 (1.07)	-0.37 (0.7)
Parahippocampal gyrus	Left	0.09 [0.03, 0.15]	0.006 (0.035)	0.04 [0, 0.08]	0.029 (0.085)	1.22 (0.55)	-0.5 (0.57)
	Right	0.11 [0.04, 0.18]	0.003 (0.030)	0.08 [0.03, 0.13]	0.002 (0.009)	2.05 (0.61)	-0.08 (0.54)
Fusiform gyrus	Left	0.08 [0.03, 0.13]	0.007 (0.036)	0.06 [0.03, 0.09]	3.8E^{-4} (0.003)	1.78 (0.53)	-0.4 (0.56)
	Right	0.11 [0.04, 0.18]	0.002 (0.022)	0.05 [0, 0.1]	0.044 (0.111)	1.36 (0.64)	-0.72 (0.57)

[a] Session estimate examined the effect of baseline versus follow-up scan in the post-lockdown test group. This parameter was used to validate that the interaction effect observed between the group stemmed from a robust effect in the test group (see methods).

[b] Volumetric change normalized to baseline scan (difference/ baseline).

with each other in our test group sample (r = -0.106, t(48) = -0.74, p = 0.463). Our reported regions demonstrated significant volumetric change above and beyond these covariates. After FDR correction, no region showed an effect of TBS. However, we did find a negative effect of TFL in the two amygdalae ROIs and the left fusiform gyrus, suggesting that the volumetric changes in these regions moderated as time following lockdown elapsed. Based on these results, we estimated the time to decay as the estimated number of days from lockdown until volumetric changes returned to normal levels, similar to those of the control group (left amygdala: β_{TFL} = -0.41, t(47) = -3.1, p = 0.003, $p_{adj.}$ = 0.048, time to decay = 95 days; right amygdala: β_{TFL} = -0.54, t(47) = -4.38, p = 6.7E-5, $p_{adj.}$ = 0.002, time to decay = 83 days; left fusiform gyrus: β_{TFL} = -0.54, t(47) = -4.44, p = 5.5E-5, $p_{adj.}$ = 0.002, time to decay = 82 days; Fig. 3).

To validate that the reported effects do not stem from potential confound in the experimental or analysis design, we run a series of post-hoc regression analyses, in which we modeled different features of the sample and potential confounding factors. These analyses assisted in evaluating the robustness of the effect of interest and validate that it remains significant above and beyond each of the potential confounds (see supplementary materials for a detailed report). Examining the impact of potential confounds related to the design of the experiment revealed that our main effect, the interaction effect of time and group, remained significant in all 10 ROIs also when including covariate of age, gender, and most importantly-volumetric values at baseline. The results also remained consistent when evaluating the volumetric change effect in log-odds units ($p_{adj.}$ < 0.05 for the interaction effect, p = NS for the other covariates and sample features, in all 10 reported ROIs).

Several statistical and experimental cofounds that were tested, resulted in a small decrease of statistical significance of the volumetric change interaction effect (see additional detailed analysis in the supplementary materials). These decreases resulted in some ROIs falling short of the statistical threshold after FDR correction ($p_{adj.}$ < 0.1; all significant before FDR correction).
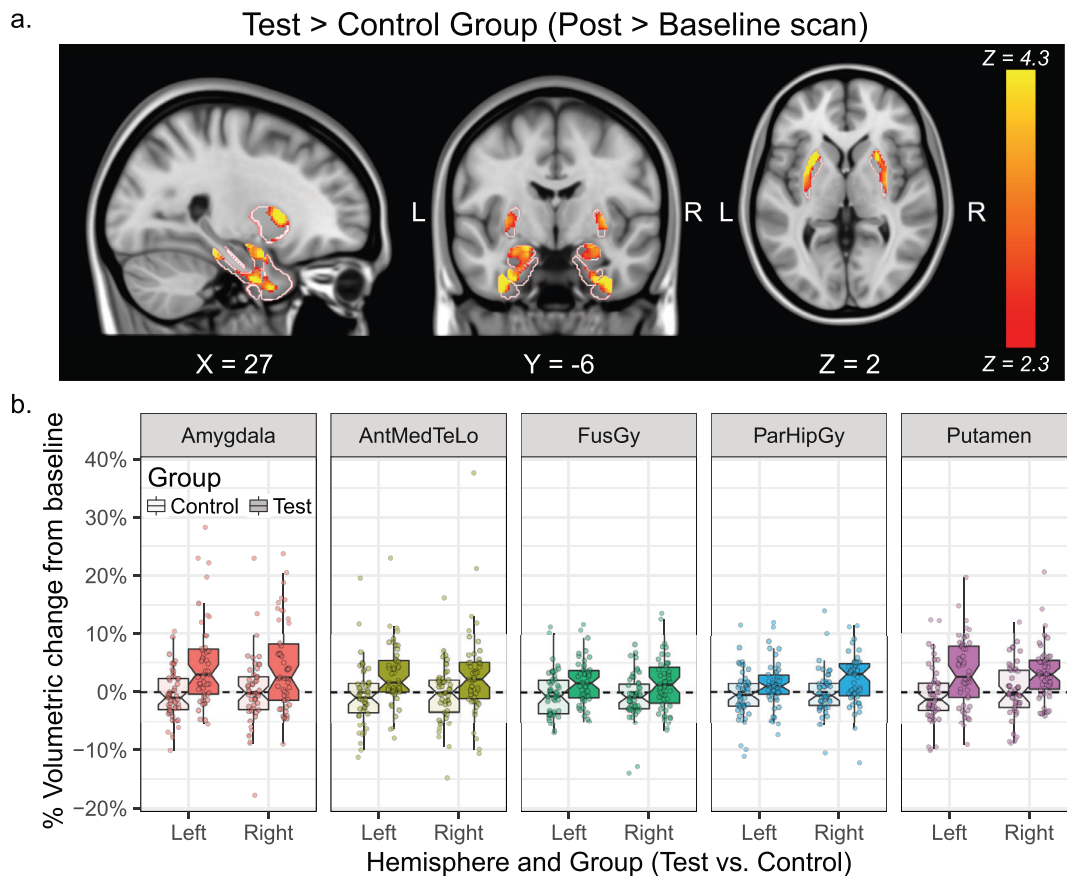
a.

b.

Fig. 2. Volumetric changes results.
An interaction effect for time (baseline versus follow-up scan) and group (test versus control) was evaluated on segmented surfaces in an SBM analysis. Significant interaction effects were observed bilaterally in the amygdala and putamen ROIs, as well as in three ventral temporal cortical ROIs. **(a)** To examine spatial patterns within the identified ROIs, a post-hoc voxel-based analysis was conducted within each ROI mask (see supplementary materials for whole brain VBM results). Light red contours represent segmentation borders of the ROIs. Red-yellow colors represents z-transformed significance of the interaction effect. **(b)** Individual distribution of the results in the control group (light colors) and test group (dark colors). For better visualization, units were normalized to baseline (difference/baseline) and presented in percentage units (see supplementary materials for plot in non-normalized units). Box-plot center, hinges, and whiskers represent the median, quartiles, and $1.5 \cdot IQR$ from the hinges, respectively. A notch of $1.58 \cdot IQR/\sqrt{n}$ represent an estimated 95% confidence interval for medians. Dots represent individual participants. Abbreviated ROI names: AntMedTeLo = anterior temporal lobe (medial part); FusGy = fusiform gyrus, ParHipGy = Parahippocampal gyrus.

In one analysis, excluding in each ROI analysis participants with extreme volumetric change (2.5 SD from group mean) resulted in two ROIs dropping below statistical significance after FDR correction (left parahippocampal gyrus: $p_{adj.} = 0.061$, right fusiform gyrus: $p_{adj.} = 0.064$). In a second analysis we aimed to validate that the effect is consistent when accounting for the different initial-experiments that participants took part in before COVID-19 outbreak. Adding the initial experiments as an additional independent factor to the regression model resulted in reduced significance of the interaction effect showing larger volumetric change in the test group, within 5 ROIs (right amygdala: $p_{adj.} = 0.065$, left parahippocampal gyrus: $p_{adj.} = 0.098$, right parahippocampal gyrus: $p_{adj.} = 0.073$, left Putamen: $p_{adj.} = 0.098$, left Putamen: $p_{adj.} = 0.068$; all $ps < 0.05$ before FDR correction, $p_{adj} = NS$ for the initial-experiment confound factor). Including the scan-angle used in the initial experiment as a factor resulted in similar outcomes, with six ROIs dropping below statistical significance threshold after FDR correction (right amygdala: $p_{adj.} = 0.058$, right anterior temporal lobe (medial part): $p_{adj.} = 0.058$, left parahippocampal gyrus: $p_{adj.} = 0.074$, right parahippocampal gyrus: $p_{adj.} = 0.058$, left Putamen: $p_{adj.} = 0.074$, left Putamen: $p_{adj.} = 0.058$; all $p < 0.05$ before FDR correction; $p_{adj.} = NS$ for the scan-angle factor).

A potential explanation for this small decrease in significance of the group-time interaction effect could be due to the imbalanced design. The pool of participants who were included in the study's test and control group consisted of one completed study (Botvinik-Nezer et al., 2020) and three additional ongoing experiments that have been running before COVID-19 outbreak. The allocation for test and control group was highly related to the initial-experiments in which participants took part in ($\chi^2_{(3)} = 54.44$, $p = 9.0E^{-12}$, Nagelkerke pseudo-$R^2 = 0.56$; logistic regression examining the association of test group allocation and initial-experiment, see methods). In two of the initial-experiments, participants scans were aligned to the anterior-commissure posterior-commissure (AC-PC) line, while in the other initial experiments, participants were scanned in 30° angle of the AC-PC line. Nonetheless, the interaction effect of time and group overall remains consistent ($p_{adj.} < 0.1$, before FDR correction all $p < 0.05$), while the initial experiments and the scan angle confounding factors were always insignificant. Thus, it is unlikely that the results were driven by these confounds.

Finally, in a post-hoc analysis we reanalyzed the results using CAT12 VBM pipeline. Using voxel-based instead of surface-based analysis resulted in similar results within the amygdalae and temporal cortices ROIs, while no significant effect was found in the bilateral Putamen ROIs. A significant effect was observed in the adjacent nuclei of bilateral Pallidum (left Pallidum: $\beta_{interaction} = 0.185$, 95% CI [0.09, 0.29], $t(96) = 3.7$, $p_{adj.} = 0.006$; right Pallidum: $\beta_{interaction} = 0.172$, 95% CI [0.08, 0.26], $t(96) = 3.8$, $p_{adj.} = 0.005$), which was not significant in a SBM analysis. These results further support the conclusions regarding the temporal ROIs and amygdala, while destabilizing the conclusiveness
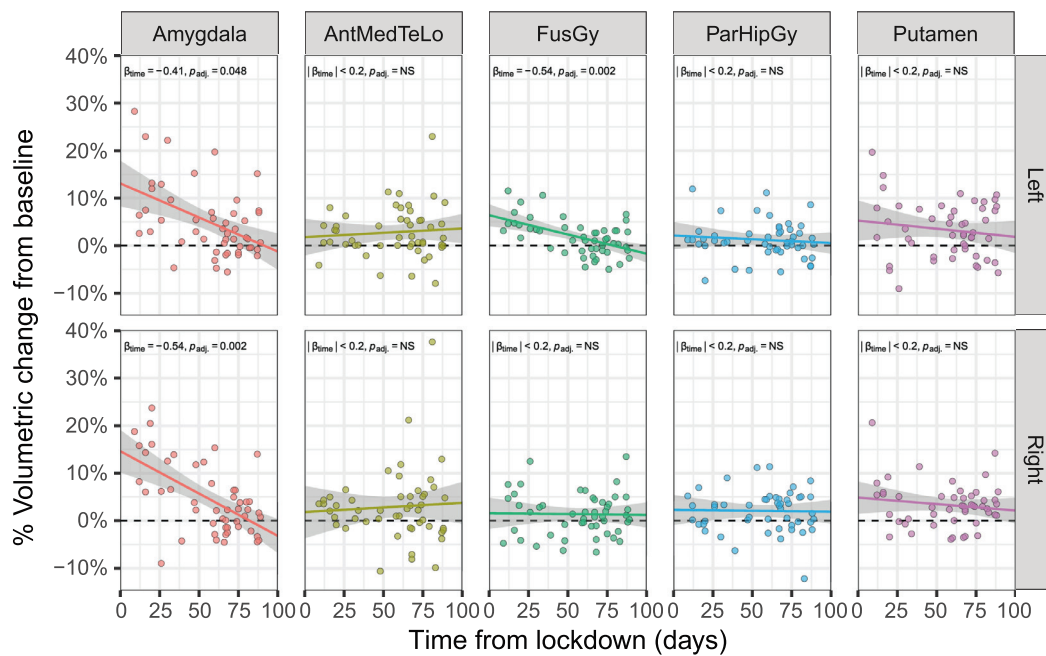
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Fig. 3. Time following lockdown effect on volumetric changes.
The time from lockdown relief until the follow-up scan session (TFL) was added as an addition covariate to the model, revealing significant effect in the two amygdalae and left fusiform gyrus. Points represent individual participants in the post-lockdown test, *p*-values were FDR adjusted for multiple comparisons. Abbreviated ROIs: AntMedTeLo = anterior temporal lobe (medial part); FusGy = fusiform gyrus, ParHipGy = Parahippocampal gyrus.

of the results in the Putamen, as changes in gray matter segmentation or another dissimilarity between the two pipelines diverted the effect in the Putamen subcortical nuclei.

In an additional exploratory analysis, we examined whether the volumetric brain changes were associated with the psychological constructs identified in our EFA, based on participants' self-reports. We used two linear models to explain the variability in each of the factors, using the volumetric changes on the 10 identified ROIs as our model features. Overall, neither one of the factors was well associated with the volumetric changes (Factor 1 model: $R^2 = 0.20$, $F(10,38) = 0.92$, $p = 0.522$; Factor 2 model: $R^2 = 0.22$, $F(10,38) = 1.10$, $p = 0.383$). Examining the contribution of individual ROIs within the models (measured as the significance of the β estimates), did not reveal a significant association with the factors for any one of the ROIs ($p_{adj.} > 0.05$; FDR correction by the number of features in the model). Also adding the two factors as covariates to the linear models examining the volumetric change effect, did not reveal significant contribution of the factor to the models. Thus, in our work we could not identify a clear association between the behavioral data and volumetric changes in our detected ROIs.

3. Discussion

Our study demonstrates that volumetric change patterns in the brain occurred following the COVID-19 initial outbreak period and restrictions in a sample of healthy participants, who were not somatically affected by the pandemic. While previous studies demonstrated brain plasticity using T1-weighted MRI following planned interventions (Maguire et al., 2000; Jung et al., 2013; Draganski et al., 2004), the current work outstands in its unique demonstration of stark structural brain plasticity following a major real-life event.

Our findings show neural changes that were not caused directly due to COVID-19 infection, but rather related to the societal effect, further resonating the mental contagiousness aspect of the COVID-19 pandemic (Valenzano et al., 2020). We show volumetric increase in gray matter in the amygdalae, putamen, and ventral anterior temporal cortices. The changes in the amygdalae showed a temporal-dependent effect, related

to the time elapsed from lockdown but not the duration from the baseline scan. It should be noted that although lockdown restrictions had initially reduced infection rates in Israel, just one month after the lockdown was lifted, the number of infected cases started to rise again and reached higher number of active infected cases by the end of data collection, compared with the peak numbers during the actual lockdown period (approximately 2,000 daily new cases by the end of July versus under 750 new daily cases during the peak of the lockdown period in April (Israel Ministry of Health, 2020), see detailed timeline in the methods section and Fig. 4). This suggests that the effects observed in the current study are less likely to be attributed to the concrete health risks of contracting the virus, but rather to the first wave of the outbreak, characterized with perceived uncertainty and substantial unexpected changes in everyday life.

Examining the contribution of study features such as volumetric measurements at baseline, the initial study, and scan angle, revealed that the volumetric change effects in the bilateral amygdalae and temporal cortical ROIs, were mostly stable. Although some confirmatory analysis with confounding covariates slightly reduced the significance of the group-time interaction effect, this decrease was relatively small (with significant results before FDR correction), and more importantly, the confounding factor were not significant in any of the models. Thus, it is unlikely that a confound related to the study design could account for the volumetric change effect. Changing the analysis pipeline from surface-based to voxel-based morphometry, resulted in non-significant effect in the Putamen; thus, suggesting that the effect in these nuclei might be susceptible to differences in analysis pipeline. Putatively, the results in these regions change due to different segmentation of the nuclei, registration or smoothing. Therefore, conclusions regarding volumetric change in the Putamen should be more reserved.

The current literature regarding volumetric changes in the amygdala following stressful events, and especially real-life events, is quite limited. Some studies found evidence in agreement with our results, such as one study which showed that a decrease in amygdala volume was associated with greater stress reduction following mindfulness training (Hölzel, 2009); while others found evidence in the opposite direction,
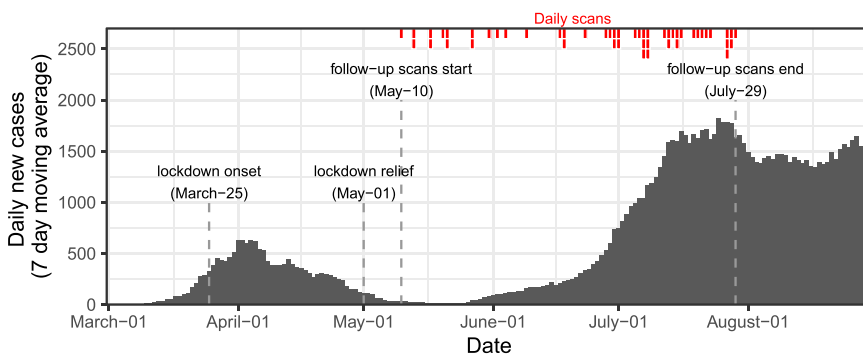
Fig. 4. Study timeline and outbreak data. On February 21st, 2020, the first COVID-19 case in Israel was recorded. Daily new cases were smoothed using 7-days moving average. Data were retrieved and modified based on the Israeli Ministry of Health reports (Israel Ministry of Health, 2020; Ritchie, et al., 2020). A lockdown was issued on March 25th, which was gradually released until the removal of the 100-meter restriction on May 1st, marking lockdown onset and relief, respectively (shorter vertical dashed line). MRI data of the test group were collected between May 10th to July 29th (longer vertical dashed line). Short bars on top (in red) represent the number of participants scanned for the study each day.

such as one study which found that smaller amygdala volumes within participants who were in closer proximity to the World Trade Center during 9/11 events (Ganzel et al., 2008), and overall meta-analyses approach often showing contradicting evidence regarding amygdala volumetric difference within population associated with stress such as post-traumatic stress disorder (PTSD) and generalized stress disorder (O'Doherty et al., 2015; Duval et al., 2015). Our results, showing a gradual decline of the volumetric change effect as a function of TFL, could provide a potential insight into these inconclusive patterns. It is possible that without time-locking to a strong external event, volumetric change effect would be more difficult to detect. This point highlights the uniqueness of our study that included a repeated session design before and after a real-world event.

The current study was in many aspects unplanned; therefore, we are left with only partial answers as to which specific behavioral or cognitive impacts of the COVID-19 outbreak led to the neural changes observed in the healthy participants who took part in our study. The involvement of the amygdala may suggest that stress and anxiety could be the source of the observed phenomenon, due to its well-recorded functional and structural associations (Ganzel et al., 2008; Hölzel, 2009; Rogers et al., 2009; Schienle et al., 2011; Mochcovitch et al., 2014; Bryant, 2008; Stevens et al., 2017). Nevertheless, it is hard to draw clear conclusions as many aspects of life have changed in this time period, and could have potentially affected different regions in the brain - from limiting social interactions, increased financial stress, changes in physical activity, work routine, and many more. The limited behavioral data collected in the current study did not provide a strong connection to the imaging results, and thus future work could try to better address the complex brain-behavioral associations in this real-life experience.

Furthermore, as our study only examined T1-weighted anatomical scans, we are limited in our scope to gross-anatomy macroscale changes. Imaging research using additional imaging methods such as diffusion tensor imaging (DTI) and functional MRI (fMRI), showed that neural plasticity processes are often characterized by changes of microstructural scale, commonly expressed in the white matter (Sagi et al., 2012; Scholz et al., 2009; Sampaio-Baptista et al., 2013; Steele and Zatorre, 2018) and functional neural activity (Brodt et al., 2018), which were not examined here. Further research combining both more extensive behavioral and additional imaging measurements might be able to link brain modifications with specific behavioral manifestations of COVID-19 outbreak.

Despite these limitations, our findings show that healthy young adults, with no records of mental health issues, were deeply affected by the outbreak of COVID-19. These findings are both ground-breaking in showing brain plasticity of subcortical regions following real-life external event, as well as in revealing an additional impact of the COVID-19 on the well-being of the general public. Our results emphasize the impact of widescale societal changes and suggest that when forming such changes, one should take into consideration the indirect impact on the general well-being of the population, alongside the efficacy of the societal changes.

4. Materials and methods

4.1. Data and code availability

Our sample size, hypotheses and analyses plan were pre-registered on the Open Science Framework (OSF), soon after data collection began, but prior to completion of the data collection and data analysis (project page: https://osf.io/wu37z/; preregistration: https://osf.io/k6xhn). All behavioral data, processed imaging data, and analysis codes are shared on the OSF project page. Uncorrected and small-volume corrected statistical maps of the voxel-based results described in the current work are available at https://neurovault.org/collections/8591/.

4.2. Participants

The study included two groups: A test group scanned before and after COVID-19 lockdown, and a control group, scanned twice before COVID-19 outbreak. All participants had no background of neurological disorders, did not show symptoms for COVID-19 and were not diagnosed as carriers of the virus. The study was approved by the ethics committee of Tel Aviv University and institutional review board (IRB) at the Sheba Tel-Hashomer medical center. Since the IRB protocol allowed us to scan the participants several times over a long period of time, we were able to collect the data from participants who were scanned prior to COVID-19 outbreak and invite them back for a follow-up scan as part of the longitudinal study they have agreed to take part in. Participants received monetary compensation for their time and gave their informed consent to take part in a longitudinal experiment aimed to examine brain plasticity across several sessions, which was initially not directly related to COVID-19 outbreak.

The test group included $n = 50$ participants who were scanned before and after COVID-19 lockdown (Δ Time between scans: $M = 309.3$, $SD = 207.5$, range $= 67$ - 1460 days; Age: $M = 30.1$, $SD = 6.65$, range $= 21–48$; Females: $n = 20$, prop. $= 40\%$). The lockdown period began on March 25th and was gradually relieved throughout late April. We mark here May 1st as the lockdown relief date, as on this day an issued 100 m movement limit for non-essential needs was lifted. The test group data collection started as soon as lockdown relief took place, for a period of approximately 3 months, until the end of July, 2020 (Δ Time from lockdown relief: $M = 57$ days, $SD = 24.62$, range $= 9–89$ days; see Fig. 4 for the study timeline).

We compared the volumetric changes of the test group to those of a control group of $n = 50$ participants, who were scanned twice before COVID-19 outbreak (Δ Time between scans: $M = 126.7$, SD $= 190.4$, range $= 21–886$ days; Age: $M = 27.4$, $SD = 5.63$, range $= 19–42$; Females: $n = 23$, prop. $= 46\%$).

The participants included in the current study took part in one of four experiments that started before COVID-19 outbreak in Tel-Aviv university imaging center. The first study was the only one completed prior to COVID-19 outbreak (Botvinik-Nezer et al., 2020), from which $n = 29$ participants were randomly sampled to be used in our control group

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sample (consisting 58% of the control group). Participants in this study were scanned twice with anatomical, functional and DW imaging in a study examining neural correlates of preference modification paradigm. A second study examined the same paradigm used in the first study, and included structural, functional, and resting state scans. A total of 41 participants were sample from this second experiment - $n = 11$ (22%) for the control group and $n = 30$ (60%) for the test group. A third study from which $n = 10$ (20%) participants were sampled for the control group and $n = 18$ (36%) were scanned in the test group, examined longitudinal changes in structural features of the brain. It included structural and DW imaging. Finally, $n = 2$ (4%) were sample for the test group, from a fourth study which examined network connectivity in the brain using structural and resting state imaging data.

As this was a unique natural experiment, some data features, including affiliation for the prior experiment, could not be balanced across the experimental groups. There was a strong dependence between the experimental groups (control versus test) and the four prior studies affiliation ($\chi^2_{(3)} = 42.1$, $p = 3.8E^{-9}$; Pearson's χ^2 test for independence), which is also quantifiable using logistic regression with the experiment group as dependent binary outcome (log-likelihood ratio test: $\chi^2_{(3)} = 54.4$, $p = 9.0E^{-12}$, Nagelkerke pseudo-$R^2 = 0.56$).

The final number of participants to be scanned for the current study was determined based on experimental and health-related considerations. From an experimental point of view, we aimed to minimize the potential confounding effect of prolonged delay from the lockdown period. In addition, the number of available participants became limited as time progressed - both of potential test group participants who were scanned not long prior to COVID-19 outbreak, as well as the number of available control participants who were scanned twice prior to the outbreak. Finally, towards the end of data collection a second wave of COVID started to form in the country, with increasing number of new COVID cases. Due to the increase of health risk for our participants, and the inevitable anticipated lockdown, we decided to stop data collection for the study at that time point. The results were not examined before imaging data collection was completed. No participants were excluded from analysis following examination of the imaging data.

4.3. Imaging data acquisition

Before COVID-19 outbreak, participants took part in several unrelated imaging studies, all performed in Tel-Aviv University's Imaging Center. Participants were scanned in Siemens Prisma 3T MRI scanner. Each scan session (both pre- and post-COVID-19) included high resolution T1w anatomical scan, with magnetization prepared rapid gradient echo (MPRAGE) sequence: TR = 1750ms, TE = 2.6ms, TI = 900ms, with a resolution of $1 \times 1 \times 1$mm (Park et al., 2020). These images were used for volumetric regional analysis by estimating the pial and inner surfaces of the cortex and projecting those into a Hammer's atlas system.

Each post-COVID session also included multi-shell diffusion-weighted echo-planar imaging (DW EPI) sequence and functional MRI scans of Resting-state data, scanned with a gradient-echo EPI (GE EPI). The diffusion weighted and functional imaging data were meant to be used in diffusion tensor imaging (DTI) and resting state connectivity analyses, respectively. However, since not all test group participants were scanned with those two imaging protocols during their baseline scan session, analyzing these data would require a different approach than the one we used in the current study to analyze structural changes with T1w-images. We decided that the analysis of these data is beyond the scope of the current manuscript and thus have not examined it at the current time point.

4.4. Statistical modeling

Volumetric change was evaluated separately for each of the 58 relevant ROIs from the Hammers Atlas in a linear regression model. For simple interpretation and modeling, we used the difference in volume measurements between the two scans (volumetric change) as the dependent variable. The volumetric change observed for each individual was modelled using a group indicator (0-Control, 1-Test), Time between scans (TBS; mean-centered across the entire sample), and the Time following lockdown (TFL; mean-centered across the test group) independent variables. Control group participants, for which TFL was not a relevant covariate were assigned with the TFL value of 0 (same as modeling TFL as an interaction with group effect, evaluating its contribution to test-group volumetric change only). Using a difference score as the dependent variable, effectively allowed us to interpret the model's intercept as the Time main effect (baseline versus follow-up scan), and each regressor as the interaction of the independent variable with time. The analysis is identical to a linear mixed model with a random intercept for each participant, main effect of time and interaction of time with the other independent variables-e.g. the effect of the group independent variable in a model with volumetric change as the dependent variable, is identical to the group-time interaction term in a mixed effect regression model. The main regressor of interest was thus the group independent variable, indicating a significant difference in volumetric change between test and control group, while accounting for the TBS covariate in both groups and the TFL covariate in the test group.

To validate that the reported effect originated from the control group, the data of each ROI were also modelled for the subset of the test group participants only, using the same mean-centered TBS and mean-centered TFL covariates. In this analysis the main result of interest was the intercept term, indicating that the mean volumetric change of the test group was different than 0, accounting for the other covariates. We also used this model to estimate the effect of TFL, using only the information from the test group.

All p-values were corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) across the 58 regions examined. We reported regions for which a significant volumetric change was observed uniquely for the test group, which had significant group-time interaction effect ($p_{adj.} < 0.05$), as well as a significant time effect for the test group ($p < 0.05$, before FDR correction). We decided to deviate from the pre-registered analysis plan and report two ROIs which had significant interaction effect after FDR but with significant effect within the test group only before FDR correction (left parahippocampal gyrus $p = 0.029$, $p_{adj.} = 0.085$; and right fusiform gyrus, $p = 0.044$, $p_{adj.} = 0.111$), as we thought that it is worth mentioning them nonetheless due to their strong interaction effect and corresponding contralateral ROIs.

In addition to these pre-registered statistical models, we also performed several post-hoc analyses of two types. In the first family of analyses, we examined different statistical definitions of volumetric change as our dependent variable as well as added additional independent variables such as the baseline scan, in order to further validate our results and exclude potential confounds (see supplementary materials). In the second family of models, we aimed to link the volumetric change effect with our behavioral measurements by including as additional covariates the two factors that were identified in the COVID-19 questionnaire factor analysis.

4.5. Post-hoc voxel-based analysis and visualization

To provide a spatial visualization of our data, we used an additional (not pre-registered) VBM analysis. Raw images were smoothed with 12mm FWHM smoothing kernel, underwent tissue segmentation and spatial registration prior to statistical analysis. In the VBM analysis statistical significance was calculated for an interaction effect, indicating a different volumetric change in the test group versus control group. The outputted map of p-values indicating significant interaction effect, was converted to Z-values map via the normal cumulative distribution function (CDF), and then thresholded at $|Z| > 2.3$ (corresponding to $p < 0.01$).

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Table 2
COVID-19 lockdown questionnaire.

Question	Answers (%)	Binary (%)
1. Did you stay home during the lockdown, except for essential needs / did not leave at all?	0-no (20.4) 1-yes (79.6)	0-no (20.4)
	1-yes (79.6)	1-yes (79.6)
2. Did the lockdown increase your feeling of anxiety?	0-no (61.2)	0-no (61.2)
	1-yes (38.8)	1-yes (38.8)
3. With how many people did you meet during the lockdown (including people you are living with at home)?	0-none (0)	0-more than three (42.9)
	1-up to three people (57.1) 2-up to five people (22.4) 3-up to ten people (20.4)	1-up to three (57.1)
4. Do you think your behavior will change following the lockdown?	0-no (65.3)	0-no (65.3)
	1-yes (34.7)	1-yes (34.7)
5. How did your meeting with your parents' routine look like during the lockdown?	0-same as before the lockdown (34.7)	0-as before or with precautions (55.1)
	1-with precaution measurements: distancing, mask, etc. (20.4) 2-did not meet at all (44.9)	1-did not meet at all (44.9)
6. What was your employment status during the lockdown?	0-same as before lockdown (28.6)	0-unemployed / part time (42.9)
	1-full time working from home (28.6)	1-same as before / full time from home (57.1)
	2-part time working from home (8.2) 3-Furlough / unemployed (34.7)	
7. How concerned are you with the long-term effect of the lockdown, regarding yourself?	1-not at all (28.6)	0-low, score 1,2 (53.1)
	2 (24.5) 3 (30.6) 4 (14.3) 5-very concerned (2)	1-moderate-high, score 3–5 (46.9)

It is important to note that the resulting map was used for visualization and not statistical inference. It does not account for multiple comparisons correction, nor does it take into direct account the additional requirement in our main analysis pipeline, that the difference effect of the test group would also be significant above 0 (i.e. to report only effects stemming from an effect in the test group, and not from an opposite trend in the control group).

In an additional (not pre-registered) analysis, we used the VBM output as an additional validation for the reproducibility of our results. Participants' volumetric maps (one for each of the two scans) were segmented according to the Hammers Atlas ROIs. The data were averaged within each ROI and we repeated the process used to identify significant ROIs using voxel-based data, i.e., for each region the significance of the interaction effect and time effect for the test group were examined with linear models. Results were then FDR corrected for multiple comparisons, across the 58 ROIs tested.

4.6. Behavioral data collection

To evaluate participants' experience in the peak days of the COVID-19 outbreak, we asked them to think back on their experience during this time and fill out a 7-items questionnaire regarding their experience of the COVID-19 lockdown (see Table 2 for a description of the items). The questionnaires were filled out after the initiation of the study, when the lockdown's stringent 100-meters limitation was lifted, thus the results represents the participants' recalled experience of the lockdown. Most participants filled out the questionnaire on the day of the post-lockdown scan session, some filled it a few days before their second scanning session. A total of $n = 76$ participants filled out the COVID-19 questionnaire and comprised the potential pool of test group participants for the current study, out of which the first $n = 50$ who agreed to come to be scanned, were included in the imaging dataset. One participant was scanned but did not complete the questionnaire, therefore this participant's behavioral data were not used and analyses of the questionnaire were based on $n = 49$ valid participants.

4.7. Exploratory factor analysis (EFA)

Responses to the lockdown questionnaire were coded into binary responses, based on the sample median, splitting the sample into relatively similar sized groups for each item (Table 2). To identify the main themes in the questionnaire, which could be correlated with the imag-

ing data, we performed an exploratory factor analysis (EFA) on the binarized data, using the "psych" R package (Revelle, 2020).

Since EFA require large number of participants, we used the data from all available $n = 75$ participants who completed the questionnaire. Kaiser-Meyer-Olkin (KMO) factor adequacy test revealed that the 'employment' item had a very low measure of sampling adequacy (MSA; employment item's MSA = 0.26; which is far below the suggested minimal MSA of 0.528) for EFA. The 'employment' was also not loaded to any of the factors; therefore, we removed it from the final EFA model. Overall, even after removing low KMO item, our data were found to be weakly appropriate for factor analysis, with overall MSA = 0.48. Thus, considering the small sample size and low fit of the data to EFA, the results of the analysis should be interpreted with caution.

We performed polychoric correlations based EFA, which is suitable for binary variables, with two factors and Varimax rotation, assuming orthogonality between the factors. Our selection of number of factors was based on visual inspection of scree plot of eigenvalues, as well as by comparing actual data to simulations of random data matrices. Using Oblimin rotation, which allows for correlation between the factors, revealed very low correlation ($r = 0.08$), suggesting that Varimax rotation was an appropriate choice for our model.

In a previous version of this manuscript, we used principal component analysis (PCA) to identify our factors of interest, however this procedure is less appropriate than EFA, and is therefore not reported here. However, the results using PCA were fairly similar to the ones we found with EFA (previous version is available at: https://www.biorxiv.org/content/10.1101/2020.09.08.285007v2).

To examine the association of the behavioral data with the volumetric changes, while maintaining relatively limited number of multiple comparisons, we used the two factors for these analyses instead of each of the items. These two factors' scores for each participant were extracted and correlated with the change in gray matter volumetric data in our regions of interest.

Declaration of Competing Interest

The authors declare no competing interests.

Data and materials availability

All behavioral data, processed imaging data, and analysis codes are shared on the OSF project page (https://osf.io/wu37z/). Uncorrected and small-volume corrected statistical maps of the voxel-based results described in the current work are available at https://neurovault.org/collections/8591/.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118311.

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