Lesion-deficit mapping of social behavior change following focal brain lesions

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Introduction

Behaving appropriately within the context of social situations is crucial for establishing and maintaining social relationships (e.g., not joking at a funeral). This requires dynamic updating of others' beliefs, intentions, and desires (mentalizing) into social contexts to flexibly guide behavior. Lesion-case studies[1] have strongly suggested a causal role of the prefrontal cortex (PFC) in guiding social behavior. Especially, the medial PFC (MPFC) has been highlighted as a top-down regulator of context-dependent social behavior, possibly modulating a network of brain regions sensitive to social inferences, including the precuneus (PC) and temporo-parietal junction (TPJ) regions. However, it remains unclear how lesions to regions in this "social brain network"[2] affect the underlying functional and structural connectivity. This study seeks to advance our understanding of the causal role of brain regions to functional and structural brain networks underlying complex social behavior. Such advances may reveal targets for brain modulation interventions and may aid the development of personalized outcome predictions after brain damage.

We use a multi-modal lesion-deficit approach to investigate associations between change in social behavior after brain damage and three measures of the lesion: lesion location; lesion-derived functional connectivity; and lesion-derived structural connectivity. As a measure of behavior, we focused specifically on change in social (in-)appropriate behavior reported by an individual who knows the participant well and is around them frequently and across contexts. We first applied lesion-symptom mapping to identify brain lesion locations associated with an increase in socially inappropriate behavior. We then used normative connectivity data to identify functional and structural lesion-derived networks using functional and structural lesion network mapping (fLNM, sLNM), respectively.

Methods

We included participants from the Iowa Neurological Patient Registry if they sustained a first-time brain lesion after age 18, underwent structural neuroimaging, and an informant who knows the participant well was administered the Iowa Scales of Personality Change (ISPC)[3] (n = 155 (66 female), mean age = 54.9 years (SD:13.4)). A schematic of the study design is shown in Figure 1. Participants were excluded if they

had a history of psychiatric or neurological conditions prior to lesion onset. Social behavior was measured via the 'social inappropriateness' (SI) scale of the ISPC, a 30-item subjective evaluation of behavioral change before as compared to after lesion. The evaluation was completed by an individual who knew the participant well and interacted with them closely before and after the brain lesion (e.g., spouse, close friend). The behavioral metric reflected the change in extent to which a person might act improperly in social settings, with specific examples such as acting in ways they should infer would offend others or continuing a behavior after others indicate they want them to stop. Both age (R^2 = $4.24*10^{-4}$; $F_{1,153}$ = .065; p = .799) and education (R^2 = .004; $F_{1,153}$ = .581; p = .447) of participants were not significantly associated with SI.

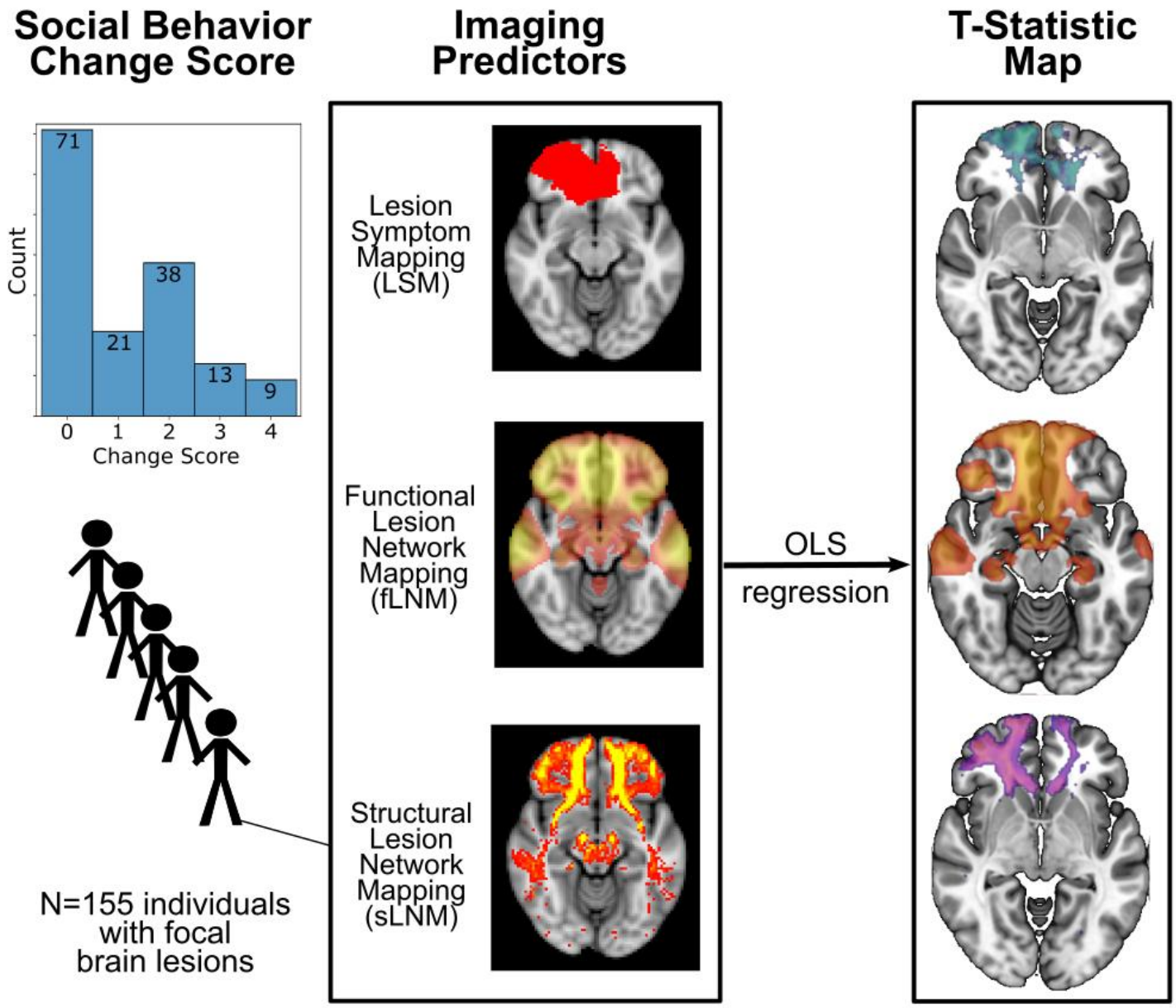

Figure 1. Schematic overview of the study. Each participant had a lesion mask outlining the boundaries of the lesion and their SI change score calculated from informant ratings. Mass univariate (Ordinary Least Squares Regression) analyses resulted in t-statistic maps of voxels significantly associated with an increase in SI across participants in this cohort. Using the same dependent variable (SI), three types of analyses were performed: LSM, fLNM, and sLNM.

Each lesion was manually traced on the participant's T1-weighted native anatomical images and transformed to MNI 152 2mm space using Advanced Normalization Tools. Since lesions impact transformation to MNI space, enantiomorphic normalization was used for unilateral lesions, replacing the lesion volume with voxel intensities from its contralesional homolog to better align the transform. Bilateral lesions were transformed by applying a cost function mask to the lesion volume, reducing the influence of voxels in the lesion volume on the transformation. The anatomical accuracy of the native

trace and transformation were confirmed and corrected, if necessary, by a neurologist blind to behavioral data.

Lesion-symptom mapping and lesion network mapping analyses were performed using the Iowa Brain-Behavior Modeling Toolkit[4] to identify brain regions and networks associated with a participant's SI change score. We conducted mass univariate Ordinary Least Squares Regression and assessed statistical significance with permutation tests (10,000 permutations) and continuous family-wise error rate correction (corrected $\alpha = .05$) with a voxel count threshold of 1,000. Lesion volume was controlled for since lesion volume was significantly associated with the SI change score ($R^2 = .10$; $F_{1,153} = 17.42$; $p < .001$).

Functional LNM generated maps for each participant using normative resting state functional magnetic resonance imaging (fMRI) data from the Genome Superstruct Project (GSP, N=1000). Each participant's lesion mask was used as a seed region-of-interest in a functional connectivity analysis, resulting in a t-statistic map of voxels functionally connected to the lesion in normative participants. A similar principle was applied for generating maps with sLNM. The participant's lesion was used as a seed in a deterministic tractography analysis using LEAD-DBS and normative diffusion MRI data from the Human Connectome Project's (HCP, N=1200) 32-fold group connectome. This resulted in a streamline map of white matter tracts connected to the lesion.

We further assessed spatial overlap between the derived fLNM maps and previously established functional brain networks for mentalizing, given the relevance of mental state inferences for socially appropriate behavior. To this end, we derived the mentalizing network using an automated synthesis of fMRI data with Neurosynth performing meta-analytic analyses of 151 previous studies using the term "mentalizing". This search term was selected to distinguish social inappropriateness from other aspects of social cognition more broadly (e.g., gaze, affective empathy, social decision-making).

Results

First, we investigated the relationship between lesion location and SI change by performing mass univariate lesion symptom mapping. This analysis revealed a set of medial frontal regions including the gyrus rectus, frontal pole, medial and orbital frontal cortex, and anterior/inferior cingulum bilaterally (Fig. 2a), consistent with prior lesion-case studies.

Second, we investigated the relationship between lesion-derived functional connectivity and SI change. Regions significantly associated with SI were present bilaterally along the medial wall of the frontal lobes, precuneus, hippocampus, parahippocampal gyrus, and cerebellar lobule IX (Fig. 2b). Additional regions included right TPJ and bilateral anterior temporal lobe (ATL). We further assessed spatial overlap between fLNM results with i) seven canonical resting-state networks[5] and ii) the Neurosynth-derived "mentalizing" task-based activation network. We found a substantial overlap between the identified SI network with i) the Default Mode (DMN, $r(155) = .329$, $p < .001$; Dice = .348) and Limbic networks (LN, $r(155) = .237$, $p<.001$; Dice = .231), as well as ii) the Neurosynth-derived 'Mentalizing' network ($r(155) = .329$, $p<.001$; Dice = .228) including the TPJ area, ATL, MPFC, cingulate cortex, precuneus, and inferior cerebellum. Voxels within the posterior cerebellum overlapped with a previously identified cerebellar Default Mode Network resting-state based parcellation[4], encompassing large portions of crus II, extending superiorly into left crus I.

Third, we used sLNM to identify white matter tracts associated with SI change after brain lesion. Findings from this analysis highlighted frontal white matter and the genu of the corpus callosum (forceps minor; Fig. 2c). Notably, sLNM findings seemed to connect regions of frontal grey matter with higher voxel intensities (i.e., t-statistic) identified using fLNM.

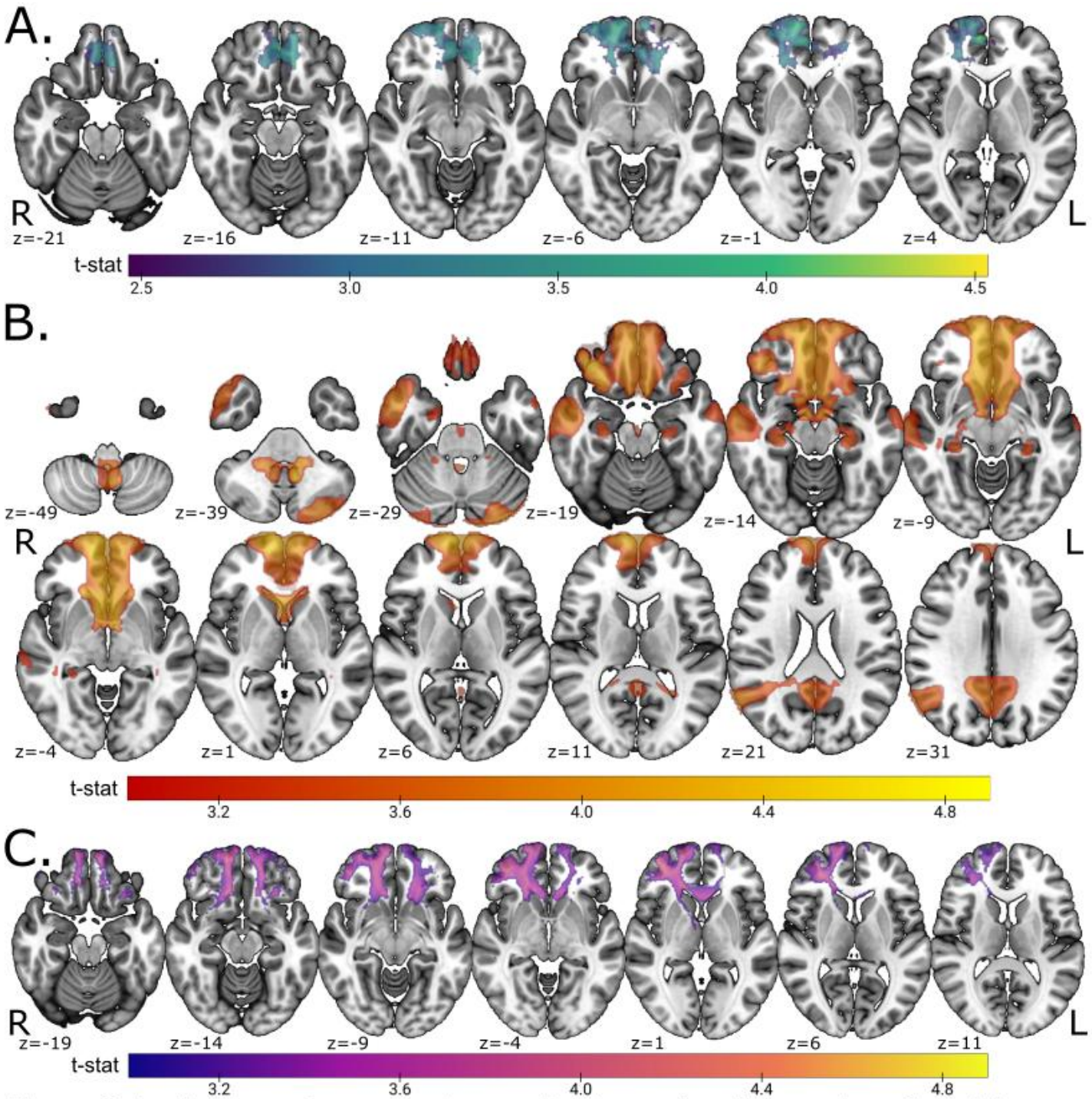

Figure 2. Lesion-symptom mapping and lesion network mapping of social inappropriateness. Voxel intensities (t-statistics) show the strength of the correlation between a given participants lesion site and an increase in SI across all 155 participants. (A) Lesion symptom mapping revealed voxels significantly associated with post-lesion SI that were stronger in the right hemisphere. (B) The strongest functional lesion network mapping findings are along the medial wall of the frontal lobe bilaterally. Significant voxels in the angular gyrus were only present in the right hemisphere. (C) Structural lesion network mapping revealed significant white matter tracts in frontal lobe, particularly in the forceps minor connecting both hemispheres.

Conclusions

This study investigated brain regions along with functional and structural networks associated with a change in social (inappropriate) behavior after a brain lesion (n = 155). The results supported prior work emphasizing the MPFC, mentalizing task network and the Default Mode resting-state network in social behavior. Extending prior work, the multi-modal lesion-deficit approach applied here further provided novel insight into the causal neurobiology by linking lesions to both functional and structural network-level disruptions. The lesion-derived functional network map was significantly correlated with the mentalizing network identified by numerous prior task-based fMRI studies. Previous research linked social / emotional personality disturbance (measured by multiple ISPC items) to a white mater region in left hemisphere adjacent to the ventromedial prefrontal cortex.[2]. Here, we show more distributed findings in MPFC, precuneus, TPJ, and ATL, specifically related to inappropriateness. Finally, posterior cerebellar involvement aligns with the hypothesis that the cerebellum contributes to higher-order cognitive and social processes, in addition to motor functions.

With regards to the MPFC, medial frontal regions are thought to be critical for self-monitoring and regulating behavior. Thus, the failure to inhibit socially inappropriate responses following damage to these regions – as indicated by the LSM results – is consistent with our general understanding of the role of MPFC. On the structural network level, interhemispheric white matter tracts (i.e., forceps minor, corpus callosum) connecting frontal regions may help facilitate coordination across more distributed social cognition networks involving posterior regions such as the temporoparietal junction regions. Together, these results suggest socially appropriate behavior depends on both localized cortical processing and long-range network communication.

Several limitations apply to this work. Inferences about associated structural and functional networks were derived from data in healthy adults, not directly by multi-modal data in the same lesion participants. Interpretation remains thus limited. While also showcasing the power of rich behavioral assessment with one single item, all analyses were based on one scale. Future work needs to investigate more nuanced (and possibly heterogenous) changes in different socio-cognitive constructs (e.g.

empathy) requiring more comprehensive assessments. Efforts addressing these limitations are currently underway.

This study provides novel insights into the distributed functional and structural networks underlying complex social behavior. In addition to advancing our understanding of the functional neuroanatomy of social behavior, these findings may contribute in the future to clinical translation, such as providing target for neuromodulation using transcranial magnetic stimulation. Identifying individuals at risk for developing chronic socially inappropriate behavior following a brain lesion could improve prognosis and guide interventions specifically aimed at social skills.

References

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