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Canceled connections: Lesion-derived network mapping helps explain differences in performance on a complex decision-making task

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Abstract

Studies of patients with brain damage have highlighted a broad neural network of limbic and prefrontal areas as important for adaptive decision-making. However, some patients with damage outside these regions have impaired decision-making behavior, and the behavioral impairments observed in these cases are often attributed to the general variability in behavior following brain damage, rather than a deficit in a specific brain-behavior relationship. A novel approach, lesion-derived network mapping, uses healthy subject resting-state functional connectivity (RSFC) data to infer the areas that would be connected with each patient's lesion area in healthy adults. Here, we used this approach to investigate whether there was a systematic pattern of connectivity associated with decision-making performance in patients with focal damage in areas not classically associated with decision-making. These patients were categorized a priori into "impaired" or "unimpaired" groups based on their performance on the Iowa Gambling Task (IGT). Lesion-derived network maps based on the impaired patients showed overlap in somatosensory, motor and insula cortices, to a greater extent than patients who showed unimpaired IGT performance. Akin to the classic concept of "diaschisis" (von Monakow, 1914), this focus on the remote effects that focal damage can have on large-scale distributed brain networks has the potential to inform not only differences in decision-making behavior, but also other cognitive functions or neurological syndromes where a distinct phenotype has eluded neuroanatomical classification and brain-behavior relationships appear highly heterogeneous.

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Keywords

lesion-derived network mapping; functional connectivity; decision-making

1. Introduction

The lesion method, in both animal models and in humans, has been highly effective at identifying brain areas that are necessary for adaptive decision-making. Neuroimaging and electrophysiology studies have corroborated lesion evidence to highlight the importance of areas such as the ventromedial prefrontal cortex, the amygdala, anterior cingulate, basal ganglia, and anterior insula in decision-making (Bechara, Damasio, Tranel, & Damasio, 1997; Clark et al., 2008; Hampton & O'Doherty, 2007; Neubert, Mars, Sallet, & Rushworth, 2015; Schultz, Tremblay, & Hollerman, 2000; Tranel, Bechara, & Damasio, 2000). These areas have been linked in the literature as a broad network of brain regions that are critical for effective decision-making (Damasio, 1996; Fellows, 2004; Kable & Glimcher, 2009). In studies using the lesion approach, patients with focal damage to specific anatomical regions within this decision-making network are studied in comparison to patients with brain damage outside the target areas of interest, to provide an index of the variability in behavior seen following “brain damage” per se and help establish the specificity of brain-behavior relationships. Needless to say, brain-behavior relationships are rarely universal (especially for complex functions), and in any given study, there are usually exceptions of the “false negative” (a patient with a lesion in a target region who does not have a deficit in the behavior of interest) and “false positive” (a patient with a lesion in a non-target, “control” region who has a deficit in the behavior of interest) types (e.g., Banich, 2004; Shallice, 1988, Chapters 9–10). Coming back to the topic at hand, the impaired decision-making behavior sometimes seen in various comparison patients is often attributed to variability that is common in brain-damaged patients, rather than a specific brain-behavior relationship. For example, if a brain-damaged comparison participant with damage to the left supramarginal gyrus has impaired performance on a complex decision-making task, this is attributed to “noise” rather than the idea that the left supramarginal gyrus is a key component in neural decision-making networks. Another possibility, however, is that impaired decision-making behavior in (at least some) such patients may reflect disruptions in neuroanatomically connected brain regions distal from the site of damage (Fornito, Zalesky, & Breakspear, 2015). An approach that can capture the broader network effects of brain injury in these cases may be more informative at probing the relationship between brain injury and disrupted decision-making behavior, and explain cases that would otherwise be anomalies not easily accounted for by prevailing theoretical frameworks.

Functional neuroimaging, specifically fMRI based resting-state functional connectivity (RSFC), has been looked at as a potential solution to investigate the broader network effects of brain injury. RSFC is typically collected while the participant lies quietly in the MR scanner, with analyses focusing on low-frequency oscillations in the blood-oxygenation-level-dependent (BOLD) response. Studies of RSFC data in healthy adults have identified functional networks known to be engaged in cognitive or affective processes. Regarding decision-making, RSFC studies have identified networks related to executive function (e.g.

the cingulo-opercular network, Dosenbach et al., 2007), salience (Menon & Uddin, 2010; Seeley et al., 2007), and valuation (N. Li et al., 2013), with these networks sharing areas of the anterior insula, anterior cingulate, amygdala, and prefrontal cortex. These regions are therefore identified in the literature as part of a broad network of regions important for adaptive decision-making.

RSFC has also shown promise for investigations with patient populations. Studies of patient populations using RSFC have typically shown differences in network characteristics between healthy adults and patients with stroke, epilepsy, traumatic brain injury, or other neurological or psychiatric disorders (Fox & Greicius 2010; Gillebert & Mantini, 2013). RSFC studies in patient samples have provided important insight into the remote effects following focal brain damage (Gratton, Nomura, Pérez, & D'Esposito, 2012; He, Shulman, Snyder, & Corbetta, 2007; R. Li et al., 2013). However, RSFC studies of patients with brain damage are also limited in that abnormal findings reflect both lesion-induced functional abnormalities as well as compensatory changes. Moreover, these techniques do not reveal the network organization of the lesion location itself, as the BOLD signal from this site is degraded by the lesion. Additionally, although RSFC data collection has become more commonplace in cognitive neuroscience, it is currently not a standard feature of clinical imaging, making it difficult to compile and compare patient samples.

A recently introduced technique takes a different approach to identifying the network effects of a lesion. Rather than perform functional imaging of the patients, the network information is inferred using normative data (Boes et al., 2015). This approach, which we term lesion-derived network mapping, leverages large, publicly available databases of RSFC data from healthy subjects in conjunction with neuroanatomical lesion mapping techniques. The goal of this approach is to examine overlap in not only the lesion location, but also in areas that were functionally connected with damaged tissue, as inferred by using each patient's lesion location as a region-of-interest (ROI) for a RSFC analysis using healthy RSFC data. In an initial application, this approach looked at four separate lesion syndromes caused by subcortical strokes. In each syndrome, ranging from hallucinations to aphasia to central pain, the heterogeneously distributed lesions showed little overlap in the lesion location, but showed high levels of overlap in functional connectivity to a common cortical region implicated in symptom expression. As a further analogy for this approach, it may be unclear at first glance why storms in Atlanta, Georgia, would cancel a flight between sunny Cedar Rapids, Iowa and Detroit, Michigan, while other storms along the East Coast have no effect on this flight. However, by looking at the connections, we see that Atlanta is a central hub for both Cedar Rapids and Detroit. Similarly, while damage to lateral occipital cortex, or damage to middle temporal gyrus may not initially predict impairments in decision-making, looking at the connections the lesion area makes to other regions implicated in decision-making may help to explain the presence of a decision-making deficit in one patient, but not another.

Here, to address the unresolved question of why some patients with lesions outside the conventional “decision-making network” are impaired on decision-making tasks, we used lesion-derived network mapping in a sample of patients with heterogeneous lesions outside the vmPFC, amygdala, or insula, who were either unimpaired or impaired on the Iowa

Gambling Task (IGT). We predicted that patients who were impaired on the IGT would show lesion-derived network connectivity overlap in the insula, ventromedial prefrontal cortex, and amygdala, and other brain areas important for generating and utilizing emotions for decision-making (Damasio, 1996). In contrast, patients who had unimpaired performance on the IGT were predicted not to have overlap in lesion-derived network connectivity maps in brain areas important for emotion-guided decision-making.

2. Methods

2.1 Participants

We identified 29 right-handed patient participants from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa (Iowa City, IA) who had a) previously completed the ABCD' version of the IGT, and b) damage outside the vmPFC, amygdala, or insula. We refer the reader to Gläscher et al. (2012) for additional details about the Patient Registry and the larger cohort of patients with IGT data from which we selected participants for the current study. Classification of damage as falling outside the vmPFC, amygdala, or insula was based on neuroanatomical classification at the time of lesion mask creation (see section 2.2 below), as well as visual inspection of neuroanatomy in each potential participant to confirm the lesion was outside of these areas. Behavioral data from all participants were collected in the chronic epoch of recovery following brain damage, at least three months after lesion onset. All participants gave written informed consent. Prior uses of the lesion-derived network mapping technique focused on clear classification of patients as either "impaired" or "unimpaired"; we therefore wanted to similarly categorically classify our patients on the basis of their IGT performance. To do this, we followed previous literature on classifying IGT performance (Denburg, Tranel & Bechara, 2005) and labeled participant performance as 'impaired' or 'unimpaired' based on the total net score on the IGT (defined as a net score +16, or -16, respectively). Participants with a net IGT score above the cut-off for impaired and below the cut-off for unimpaired performance were labeled as 'borderline' because their performance was not significantly greater or lesser than chance (as assessed by the binomial test). Classifying our sample this way, we identified 8 participants as having 'impaired' IGT performance, 11 participants as having 'unimpaired' IGT performance, and 10 participants as having 'borderline' IGT performance. The demographic and neuropsychological characteristics of all participants are presented in Table 1. A one-way ANOVA for all demographic factors indicated no significant differences between the three groups, except for Controlled Oral Word Association test (COWA) performance [$F(2,26)=3.825, p=.035$]. Since interpreting decision-making ability in the borderline group as categorically impaired or unimpaired is equivocal, and the three groups were largely indistinguishable with regards to neuropsychological and demographic characteristics, we excluded the borderline cases from our subsequent analyses and limited our analysis to the impaired and unimpaired participants. This left a final sample of 19. Because net score is only one way of presenting IGT performance, we also examined the net score (defined as the number of cards chosen from 'bad' decks A and B subtracted from cards chosen from 'good' decks C and D) of these groups across each 20-trial block of the task. These data are presented in Figure 1, and show a block-by-block divergence between our impaired and unimpaired groups. There was a significant difference in the average net score between the

impaired and unimpaired groups at block 1 [$t(17)=-2.90$, $p=.010$], such that the unimpaired group has a higher net score for the initial block. Importantly, in testing the interaction of group by block in a mixed-effects ANOVA, we found a significant interaction between group and block [$F(4,14)=3.76$, $p=.028$], supporting observed divergence in IGT performance between our two groups similar to that seen in other studies of IGT performance (Bechara, Damasio & Damasio, 2003; Bechara, Tranel, & Damasio, 2000; Denburg et al., 2005).

2.2 Lesion Analysis

Neuroanatomical analyses of lesion location and size were based on CT or MR images collected in the chronic epoch of recovery. Brainvox was used to create a 3D reconstruction of each brain lesion (Frank, Damasio, & Grabowski, 1997), which was then manually warped to a custom normal template brain using the MAP-3 technique, consistent with previous studies (Damasio & Damasio, 1989; Damasio & Frank, 1992; Fiez, Damasio, & Grabowski, 2000). In four participants, MAP-3 traces were unavailable. In these cases, the participant's lesion was manually traced on the native space high-resolution MRI image, and diffeomorphically warped to a custom normal template brain using a Symmetric Normalization algorithm (Avants & Gee, 2004). Once transferred to template space, the template brain was diffeomorphically warped to the MNI152 standard 1mm T1-weighted atlas (Collins, Neelin, Peters, & Evans, 1994; Evans, Dai, Collins, Neelin, & Marrett, 1991; Mazziotta et al., 2001), using a Symmetric Normalization algorithm. This transform from lesion template to MNI152 space was applied to each lesion map to register it to a conventional standard space used by many researchers. Lesion maps in standard space were processed with FSL software package utilities (FSL 5.0.2.2, FMRIB's Software Library) to generate lesion overlap maps of our participants. Each lesion and lesion mask was visually inspected to ensure the anatomical accuracy of transforming the lesion volume from native to MNI152 space.

2.3 Lesion-derived network mapping

To investigate which brain areas might be functionally connected with the region affected by lesion damage, we employed lesion-derived network mapping. This approach uses publicly available healthy subject RSFC data to infer the areas that would be connected with the lesion area in healthy adults. This approach is conceptually similar to the technique described by Boes et al. (2015), but with minor differences in terms of the functional imaging dataset and processing pipeline used, as well as the use of subtraction analysis of the network results. For our functional imaging dataset, we used publicly available resting-state data from 198 participants (75M/123W, Age range: 18–30) in the Cambridge Buckner Release of the 1000 Functional Connectomes Project, (http://fcon_1000.projects.nitrc.org/), with the following parameters: (slice dimensions = $3 \times 3 \times 3$ mm, TR = 3000ms, 119 volumes, TE = 30 ms). RSFC analysis on this data set was conducted in FSL (FMRIB's Software Library 5.0.2.2), AFNI (Cox, 1996), and MATLAB (2014b, The MathWorks, Inc.) using established preprocessing and analytical steps for resting-state data (Rigon, Duff, McAuley, Kramer, & Voss, 2015; Van Dijk et al., 2010; Voss et al., 2010; Voss et al., 2012). Briefly, data underwent standard brain extraction, motion correction (AFNI's 3dvolreg function), and spatial smoothing (6 mm full-width-half-maximum, using FSL), and temporal

filtering ($0.008 < f < 0.08\text{Hz}$, using AFNI's 3dBandpass function). Following preprocessing, further potential sources of noise were corrected for by extracting and regressing the mean time series from white matter, cerebrospinal fluid, and a global brain mask (representing the mean whole brain signal). In addition, the six head motion parameters described above were bandpassed with the same temporal filter applied to the fMRI data and included as nuisance regressors (Hallquist, Hwang, & Luna, 2013). Together, the 9 bandpassed nuisance regressors (white matter, CSF, global, and 6 motion parameters) were entered into a multiple regression as independent variables predicting the preprocessed rsfMRI data (using FSL's FEAT tool). Finally, the data were motion "scrubbed" following established recommendations (cf. Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). This residual fMRI volume was then used for the region-of-interest (ROI) based functional connectivity analysis and statistics.

Each lesion mask in standard space was used as a seed ROI for RSFC analysis in 198 healthy imaging datasets. The seed maps from individual subjects were concatenated to form a 4D image file (subject as the fourth dimension) and this 4D image was input to a between-subjects ordinary least-squares (OLS) regression using FSL's flameo (Beckmann, Jenkinson, & Smith, 2003). Multiple comparisons for the resulting group-level statistical maps were controlled by thresholding group contrast maps at $Z > 2.33$, with cluster correction of $p < .05$ (Worsley, Evans, Marrett, & Neelin, 1992). This lesion-derived connectivity map for each participant was binarized, and the binarized maps were summed across participants to generate overlap maps demonstrating the areas commonly functionally connected with the lesion ROIs for patients with impaired or unimpaired IGT performance (Figure 2).

Additionally, we used the PM3 method (Rudrauf et al., 2008), to directly examine the difference between IGT impaired and IGT unimpaired lesion-derived network overlap maps. Briefly, each network overlap map was divided by the total number of participants in the group, and the proportional map for participants with a lesion but without a behavioral deficit was subtracted from the proportional map for participants with a lesion and a behavioral deficit. Positive values reflect a greater proportion of participants with both lesion-derived network overlap and impaired IGT performance, relative to participants with lesion-derived network overlap and unimpaired IGT performance.

Finally, we also used each participant's lesion map and lesion-derived connectivity map in a Voxel-Lesion-Symptom-Mapping (VLSM) analysis, to identify areas where the lesion, or lesion-derived connectivity map, was significantly associated with impairment on the IGT. VLSM analyses were performed using non-parametric mapping software as implemented in the MRIcron software package (<http://www.mccauslandcenter.sc.edu/mricron/npm/>). The voxelwise Lieberman test was used to compare impaired and unimpaired lesion masks or lesion-network maps, respectively. A critical threshold of 10% was applied, such that voxels were ignored if they were not involved in at least 10% of cases. To correct for multiple comparisons, we applied a False Discovery Rate (FDR)-corrected $p < .05$ to threshold the resulting Z-maps (Rorden, Karnath, & Bonilha, 2007).

For the lesion-derived network maps, PM3 map, and VLSM results, coordinates of peak overlap were identified using FSL's clustering algorithm (15 local maxima per cluster, minimum distance between local maxima of 10mm, minimum cluster size of 2 voxels).

3. Results

We classified each participant's behavior on the IGT as impaired or unimpaired, based on their total net score, in accordance with prior studies of IGT behavior (Denburg et al., 2005). Lesion overlap maps of impaired and unimpaired groups are shown in Figure 3. In both impaired and unimpaired groups, the lesions are widely dispersed and largely non-overlapping (max overlap in each group is 2 participants, out of 8 impaired and 11 unimpaired participants, respectively). In contrast to the diffuse lesion overlap maps, lesion-derived network overlap maps show greater divergence between IGT impaired and unimpaired participants (Figure 4). In partial support of our predictions, participants who were impaired on the IGT showed maximum overlap in lesion-derived network maps with brain areas important for generating and utilizing emotions for decision-making, including the left and right insula and somatosensory cortices (Figure 4A, Table 2). In contrast, participants who were unimpaired on the IGT showed maximum overlap in their lesion-derived network maps in lateral and dorsal occipital regions (Figure 4B, Table 3). These occipital areas were also observed to show overlap in lesion-derived network maps for IGT impaired participants.

In order to more explicitly test the differences in lesion-derived network maps between IGT impaired and IGT unimpaired groups, we ran a proportional subtraction analysis of IGT impaired – unimpaired lesion-derived network overlap maps (Figure 5, Table 4). The proportional subtraction maps corroborate the differences seen in the separate group lesion-derived network overlap maps. Specifically, we observed that patients who were impaired on the IGT have lesions that are proportionally more connected with the insula, somatosensory, and motor cortices, while patients who were unimpaired on the IGT showed proportionally greater lesion-derived network overlap in middle and inferior temporal cortex, as well as lateral parietal and posterior cingulate areas.

Finally, we also ran VLSM analyses of the lesion masks and lesion-derived network maps in the impaired and unimpaired participants to test for areas where IGT impairment was associated with the presence of a lesion (for lesion maps), or lesion-derived connectivity (for lesion-derived network maps) (Figure 6, Table 5). Running the traditional VLSM analysis on lesion maps showed no areas where the lesion damage was significantly associated with impaired performance at FDR-corrected $p < .05$. Looking at the unthresholded statistical map, we observed one area in left secondary visual cortex that is moderately associated with impaired IGT performance (Figure 6A). VLSM analysis using lesion-derived network maps did not show areas significantly associated with impaired performance on the IGT after correction for multiple comparisons was applied. Looking at the unthresholded VLSM map, we observed the strongest association between lesion-derived connectivity and impaired IGT performance in areas that corroborate the proportional subtraction findings (Figure 6B). Specifically, we observed areas in the insula, somatomotor, and secondary visual cortices as strongly associated with impaired IGT performance.

Finally, given the many cognitive and affective functions ascribed to the insula, we wished to detail further how the current results might fit with findings from previous studies regarding the role of the insula in decision-making. Focusing on the right insula region identified in our PM3 analysis, we overlaid our insula cluster on a previously published connectivity-based parcellation of the insula (Figure 7), divided into posterior, dorsal anterior, and ventral anterior sub-regions (Chang, Yarkoni, Khaw, & Sanfey, 2013; maps downloaded from NeuroVault.org). This same parcellation was used in a recent literature review to remap prior studies of the insula during different aspects of decision-making (Droutman, Bechara, & Read, 2015). We observed overlap of our insula cluster within Chang and colleagues' (2013) posterior insula parcellation, although we note that our cluster borders the boundary of the posterior insula parcellation and the posterior edge of the dorsal anterior insula.

4. Discussion

We used lesion-derived network mapping to investigate patients with non-overlapping focal brain damage classified as having impaired or unimpaired decision-making on the IGT. We found that patients who had impaired decision-making had lesions at sites with network connectivity to somatosensory, motor, and insular areas, to a greater extent than patients with unimpaired decision-making. Traditional lesion mapping did not show clear differences in anatomical overlap in lesion distribution between patients who were impaired on the IGT compared to patients who were unimpaired on the IGT.

We did not observe overlap in the ventromedial prefrontal cortex (vmPFC) or the amygdala in lesion-derived network maps of patients impaired on the IGT. We had predicted lesion-derived network connectivity with these areas considering the robust evidence from studies showing the involvement of the vmPFC and amygdala in performance on the IGT (Bechara et al., 1997, 2000, 2003; Gupta, Kosick, Bechara & Tranel, 2011). At one level, this may not be surprising, as our study mainly included patients with damage concentrated to the posterior half of the brain, with most patients showing damage to sensory regions. Although we did not observe lesion-derived connectivity with vmPFC or amygdala areas, we did observe lesion-derived connectivity in our impaired participants with areas in the supramarginal gyrus and insula that map to areas previously identified in lesion and neuroimaging studies examining the cortical mapping of emotion (Adolphs, Damasio, Tranel, & Damasio, 1996; Damasio et al., 2000; Pessoa, 2008). Impaired IGT performance in these participants may therefore reflect disruptions in connections with areas important for the generation or recall of affective information during complex decision-making, instead of vmPFC areas important for binding and evaluating affective information.

The insula has also been previously identified as important in effective decision-making behavior. Specifically, the insula is often associated with avoiding potential losses during adaptive decision-making. Evidence from participants with brain damage has shown impaired decision-making following damage to the insula (Clark et al., 2008; Clark, Studer, Bruss, Tranel, & Bechara, 2014; Weller, Levin, Shiv, & Bechara, 2009), and functional neuroimaging studies have found insula activation in the context of weighing losses and risky outcomes (Kuhnen & Knutson, 2005; Rudolf, Preuschoff, & Weber, 2012). The insula is also known to be strongly associated with interoception, salience detection, and emotional

awareness (Craig, 2009), and in this context, is thought to integrate affective information with evaluations of risk or uncertainty during decision-making (Singer, Critchley, & Preuschoff, 2009). In addition, the anterior insula, along with the inferior parietal sulcus (IPS), have been identified as important nodes in a multiple-demand network linked with executive functioning and complex behavior (Duncan, 2006; 2010). However, a follow-up analysis comparing the right insula cluster identified in our subtraction analysis with a connectivity-based insula parcellation (Chang et al., 2013) indicated our cluster was located within the posterior insula, and at the border of the dorsal anterior insula. A recent review that remapped findings from various studies onto this insula parcellation showed that the posterior insula sub-region was particularly involved with signaling homeostatic balance and urge processing when evaluating stimuli (Droutman et al., 2015). Meanwhile, the dorsal anterior insula was identified as more involved with tracking risk and variance during stimuli evaluation, but also important in salience processing and attention refocusing, as well as error-monitoring when processing decision outcomes. Considering the insula and somatosensory areas together, the current lesion-derived network data suggest that in our subset of patients, impaired behavior on our decision-making task might reflect disruptions in connectivity with brain areas critical for effectively generating and using emotions during complex decision-making.

Our findings of common overlap in lesion-derived connectivity maps, but not anatomical lesion overlap, complement the longstanding observation that brain damage in one area can disrupt functions at sites remote from the damage. This idea is well embodied by von Monakow's concept of 'diaschisis' (Feeney & Baron, 1986; von Monakow, 1914), describing the changes in cognition and behavior that can result following ischemic stroke to anatomically connected, but undamaged brain regions. While most commonly associated with a transient state of disruption (the term diaschisis coming from the Greek meaning "shocked throughout"), von Monakow also referred to *diaschisis protractiva* for remote effects that do not diminish over time following damage (Feeney & Baron, 1986; Finger, Koehler, & Jagella, 2004). The concept of diaschisis has evolved in the recent literature to include consideration of the remote effects of damage to areas that are functionally connected in the same brain network, but may not have direct anatomical connections (Carrera & Tononi, 2014; Fornito et al., 2015). Likewise, different 'types' of diaschisis have been proposed to differentiate between abnormalities in remote neuronal recruitment versus disrupted connectivity between nodes in brain networks (Carrera & Tononi, 2014). While our current data cannot speak to the latter distinction, our lesion-derived network mapping approach may provide a window into the areas most likely to be affected in the context of chronic diaschisis, and provide insight into common behavioral phenotypes in the presence of non-overlapping neuroanatomical damage.

Some limitations of the current study should be noted. A limitation of lesion-derived network mapping is that this approach does not allow us to look at how reorganization following damage might play into the observed behavioral deficits. While the present results indicate that looking at the connectivity profile of the lesion area in healthy adults is informative, they cannot speak to whether maladaptive changes following focal damage (for example, recruitment of brain areas not typically involved in decision-making behavior) may also result in impaired behavior on our decision-making task. Future studies could

investigate this by collecting RSFC data in these patients, to understand how their networks may have reorganized following damage.

Additionally, the brain damage observed in our sample, while relatively confined to the cortical surface, is rarely confined to gray matter alone. The disruption of communicating white matter tracts may also play a role in disrupted behavior on our decision-making task. Although the extent of white matter damage does not appear to significantly differ between the impaired and unimpaired groups we studied, at present, we cannot rule out this factor. One potential extension of the current work to address this issue would be to analyze these lesion groups in conjunction with publicly available DTI datasets, to explore the overlap in probabilistic tractography of fibers passing through these lesions (Kuceyeski, Kamel, Navi, Raj, & Iadecola, 2014).

Another limitation of the present study is our relatively modest sample size. In the current study, we excluded patients with focal damage to the vmPFC, amygdala, and insula. Prior studies have already identified a close lesion-deficit relationship in IGT performance in patients with focal brain damage to the vmPFC (Bechara et al., 1997, 2000), amygdala (Bechara et al., 2003) and insula (Tranel et al., 2000), limiting the additional information yielded from lesion-derived network mapping in these cases. Furthermore, utilizing our lesion-derived network mapping approach in patients with highly overlapping patterns of damage is actually not informative, since seeding lesions with highly similar anatomical patterns of damage results in highly overlapping corresponding lesion-derived networks. For example, in a sample of 10 patients with vmPFC damage, lesion-derived network mapping shows the default mode network connected with the lesion in all cases, since in all patients the lesion includes the anterior prefrontal node of the default mode network. Our application of lesion-derived network mapping is probably best suited to situations where the overlap in lesion anatomy is low between patients, and variance in behavioral performance is high. For all of these reasons, we excluded cases with highly overlapping anatomical damage in the vmPFC, amygdala, and insula. We would note that our numbers for both impaired and unimpaired patient groups are typical of much neuropsychological research, and we did not observe significant differences in demographic or neuropsychological measures between our groups. Nonetheless, it is important to replicate these findings in additional patients with focal damage in various parts of the telencephalon.

A final note is that the IGT is one of several tasks used commonly to measure decision-making. Specifically, the IGT is a complex measure of decision-making, involving both decisions under risk and ambiguity, and is not readily decomposable into distinct components (Schonberg, Fox, & Poldrack, 2011). As such, we cannot speak directly to the question of which components of decision-making, such as valuation, choice selection, or other processes might be specifically impaired in our patients. It will be important to examine if the current findings apply in the context of other decision-making tasks, and if the pattern of behavioral impairment in decision-making matches the processes we would expect based on overlap in lesion-derived network maps. For example, we would expect our impaired IGT group to show disruptions in betting behavior on a risky-decision-making task similar to that of patients with insular lesion damage (Clark et al., 2008), based on the lesion-derived network overlap in that area. Future work could focus on expanding our

approach to these other decision-making tasks, as well as other cognitive and behavioral domains.

4.1 Conclusions

The current study uses a novel approach, lesion-derived network mapping, to explain differences in a group of patients with non-overlapping brain damage behaviorally classified as impaired or unimpaired on the IGT. By focusing on the remote effects that focal lesion damage can have on large-scale distributed brain networks, this approach has the potential to inform not only differences in behavior on decision-making tasks, but other cognitive functions or neurological syndromes where a distinct phenotype has eluded neuroanatomical classification and brain-behavior relationships appear highly heterogeneous.

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Figure 1. IGT performance

Iowa Gambling Task (IGT) performance for the impaired and unimpaired patient groups, graphed by trial block. Error bars represent 95% confidence interval.

Figure 2. Lesion-derived network mapping

Anatomical lesion masks in MNI space were used as seed regions-of-interest in a resting-state dataset of 198 healthy participants (**A**). We then extracted the mean cluster-thresholded ($Z > 2.33$, $p < 0.05$) connectivity map for each lesion ROI seed across the 198 subjects (**B**). The cluster-thresholded lesion-derived connectivity map for each brain-damaged participant was binarized and the binarized maps were summed across brain-damaged participants identified as impaired or unimpaired on the IGT. (**C**), creating overlap maps of lesion-derived connectivity maps for each group (**D**).

Figure 3. Lesion overlap maps

Lesion overlap maps of unimpaired (A) and impaired (B) patients on the Iowa Gambling Task. Coordinates represent the MNI z-space value for each axial slice.

Figure 4. Lesion-derived network overlap maps

Overlap map of lesion-derived connectivity networks from participants unimpaired (A) and impaired (B) on the IGT. Coordinates represent the MNI z-space value for each axial slice. IGT-impaired participants show a greater involvement of insula, somatosensory, and motor areas than IGT unimpaired participants.

Figure 5. Proportional overlap subtraction map

Proportional overlap (overlap map/group total N) subtraction map of IGT impaired-unimpaired participants. Coordinates represent the MNI z-space value for each axial slice. We observed proportionally greater overlap in lesion-derived connectivity with somatomotor and insular regions for impaired relative to unimpaired subjects.

Figure 6. Voxel-lesion-symptom-mapping

Voxel-lesion-symptom-mapping results comparing lesion masks (**A**) and lesion-network maps (**B**) for patients with impaired IGT performance to patients with unimpaired IGT performance. Coordinates represent the MNI z-space value for each axial slice. Statistical maps show voxelwise Liebermeister test results and are unthresholded. Higher Z-score indicates the voxel is associated with patient maps in the impaired group relative to patient maps in the unimpaired group.

Figure 7. Insula cluster location

Peak right insula cluster from PM3 subtraction analysis (red), overlaid on parcellation maps of the posterior insula (green), dorsal anterior insula (blue), and ventral anterior insula (yellow), described in Chang et al., 2013. Parcellation maps were downloaded from NeuroVault.org. Maps are displayed in radiological convention (left is presented on the right side of image) and slice coordinates are in MNI152 standard space.

Table 1**Demographic and Background Data**

Group	Age (SD)	Sex	Edu. (SD)	Etiology	Lesion size (%)	Chronicity (SD)	Stroop	Trails B-A	FSIQ	WCST PE	WCST Cat.	AVLT Recog.	BNT	COWA	BDI II
Impaired (N=8)	53.88 (8.18)	5W/ 3M	13.38 (1.69)	2 resection 6 stroke	0.63	5.2	51.5	38.1	103.4	13.6	5	14	53.9	32.9	8.5
Unimpaired (N=11)	53.64 (14.22)	7W/ 4M	15.09 (2.59)	4 resection 7 stroke	1.10	5.0	50.0	47.7	97.6	19.3	4.8	13.1	56.6	48.9	4.7
Borderline (N = 10)	54.90 (10.18)	4W/ 6M	13.4 (3.44)	2 resection 8 stroke	1.38	3.9	43.9	41.5	105.1	14	4.2	14	54.2	33.7	5.1

Lesion Size—percent of total brain voxels damaged; Lesion Chronicity—time since lesion onset, in years.; FSIQ—full-scale IQ from the WAIS-III (*scores from the WAIS-IV); AVLT Recog.—Auditory Verbal Learning Test Delayed Recognition Hits; WCST Cat—Wisconsin Card Sorting Test Categories completed; WCST PE—Wisconsin Card Sorting Test Perseverative Errors; COWA—verbal fluency from the Controlled Oral Word Association test; Stroop—Stroop Color-Word Interference (T-score); Trails B-A—Difference in latency (in seconds) between Trail Making Test B and Trail Making Test A; BNT—Boston Naming Test Raw Score (max score of 60); BDI II—Beck Depression Inventory-II

Table 2

Impaired Lesion-derived Network Mapping Overlap Clusters.

Region(s)	x	y	z	Max Overlap	Cluster Size
R Superior Parietal Lobule, Postcentral Gyrus, Superior Lateral Occipital Cortex	28	-58	34	8	3176
L Superior Parietal Lobule, Postcentral Gyrus, Superior Lateral Occipital Cortex	-26	-46	44	8	2013
R Insula	38	-2	12	8	1631
L Precentral Gyrus, L Superior Longitudinal Fasciculus	-34	-4	24	7	1342
L Temporal Occipital Fusiform Cortex, Inferior Lateral Occipital Cortex	-42	-48	-20	8	1197
R Inferior Temporal Gyrus, R Inferior Lateral Occipital Cortex	52	-52	-14	8	916
L Superior Lateral Occipital Cortex	-28	-70	22	7	72
L Body Of Corpus Callosum, Mid-cingulate Gyrus	-18	-26	32	7	70
R Insula	34	-16	12	7	45
L Insula	-36	-6	8	7	26
L Body Of Corpus Callosum	-14	4	30	7	13
R Posterior Corona Radiata	20	-28	34	7	7
R Inferior Longitudinal Fasciculus	42	-38	10	7	7
R Superior Corona Radiata	18	-16	38	7	4

Note: x, y, and z refer to peak cluster coordinate in 2mm MNI space; R = right, L = Left; Max Overlap is the number of overlapping participants; Cluster size is in voxels.

Table 3

Unimpaired Lesion-derived Network Mapping Overlap Clusters.

Region(s)	x	y	z	Max Overlap	Cluster Size
L Middle Temporal Gyrus, Inferior Lateral Occipital Cortex	-58	-60	-2	9	1339
R Superior Parietal Lobule, Superior Lateral Occipital Cortex	26	-46	38	9	1043
R Inferior Lateral Occipital Cortex	52	-66	-2	9	845
L Superior Corona radiata	-22	-4	26	8	105
R Supracalcarine Cortex, Forceps Major	24	-70	16	8	55
R Superior Corona Radiata	28	2	24	8	32
R Superior Lateral Occipital Cortex	24	-72	30	8	13
R Superior Longitudinal Fasciculus	30	-36	26	8	5
R Precentral Gyrus, R Cerebral WM	28	0	44	8	4
L Superior Parietal Lobule	-28	-48	42	8	2

Note: x, y, and z refer to peak cluster coordinate in 2mm MNI space; R = right, L = Left, WM = White matter; Max Overlap is the number of overlapping participants; Cluster size is in voxels.

Table 4

Proportional Overlap Subtraction Mapping Clusters

Region(s)	x	y	z	PM3 value	Cluster Size
L Precentral Gyrus	-56	6	44	0.602	380
R Insula	38	-2	12	0.545	253
L Superior Longitudinal Fasciculus, Postcentral Gyrus, Superior Parietal Lobule	-34	-36	28	0.420	206
L Temporal Fusiform Cortex, Temporal Occipital Fusiform Cortex	-42	-44	-20	0.636	165
R Superior Longitudinal Fasciculus, Postcentral Gyrus	38	-32	28	0.420	140
R Inferior Temporal Gyrus	56	-56	-10	0.545	83
R Precentral Gyrus	56	2	50	0.511	40
L Inferior Longitudinal Fasciculus	-40	-56	2	0.545	39
R VI Cerebellum	18	-56	-18	0.534	37
L V Cerebellum	-28	-42	-26	0.534	30
R Posterior Temporal Fusiform Cortex	44	-38	-18	0.477	27
L Insula	-36	-6	8	0.420	26

Note: x, y, and z refer to peak cluster coordinate in 2mm MNI space; R = right, L = Left; PM3 value reflects the proportional subtraction between the impaired-unimpaired maps, with higher positive values indicating greater damage in participants with impaired IGT performance, relative to participants without impaired IGT performance. The 99th percentile value of the PM3 map (0.3864) was used as the clustering threshold. Cluster size is in voxels, and clusters smaller than 25 voxels are not listed.

Table 5

Voxel-Lesion-Symptom Mapping Clusters

Region(s)	x	y	z	Z-Score	Cluster Size
L Temporal Fusiform Cortex	-42	-44	-20	2.47	49
R Inferior Temporal Gyrus	56	-56	-10	2.47	5
R Insula	38	-2	12	2.47	4
R Inferior Longitudinal Fasciculus	44	-42	-10	2.47	3
R V Cerebellum	12	-50	-10	2.37	3
L Inferior Fronto-Occipital Fasciculus	-36	-16	-14	2.50	3
L VI Cerebellum	-28	-46	-26	2.37	3
R V Cerebellum	12	-56	-12	2.37	2

Note: x, y, and z refer to peak cluster coordinate in 2mm MNI space; R = right, L = Left; Z-score is uncorrected for multiple comparisons. Clustering was applied to the unthresholded VLSM map with a cutoff of $Z > 2.33$. Cluster size is in voxels.