Title: Lesions that Cause Psychosis Map to a Common Brain Circuit in the Hippocampus

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Abstract: Identifying the anatomy of circuits causal of psychosis could inform treatment targets for schizophrenia. We identified 155 published case reports of brain lesions that caused new-onset psychosis. We mapped connectivity of these lesions using a normative human fMRI connectome. Lesions causing psychosis mapped to a common brain circuit defined by functional connectivity to the posterior subiculum of the hippocampus. This circuit was consistent both across individual symptoms of psychosis (delusions, hallucinations, and thought disorders), and when excluding lesions that touched the hippocampus. In an independent observational study (n=181), lesions connected to this circuit were preferentially associated with psychotic symptoms. A location in the rostromedial prefrontal cortex with high connectivity to this psychosis circuit was identified as a potential target for transcranial magnetic stimulation. Based on these results, we conclude that lesions that cause psychosis have common functional connections to the posterior subiculum of the hippocampus.

Main Text:

INTRODUCTION

Symptoms of psychosis — delusions, hallucinations, and disorganized thought — contribute significantly to global disease burden (*1*). Existing pharmacological treatments can be incompletely effective and often have intolerable side effects (*2,3*). Localizing the cause of psychosis to specific neuroanatomy could guide neuromodulatory treatment.

One approach to mapping neuroanatomy of psychosis is with neuroimaging correlates in patients with schizophrenia, a disease defined by chronic psychosis. Functional neuroimaging studies in schizophrenia have reported global dysconnectivity as well as aberrancy in default mode and frontoparietal networks (*4–7*). Structural neuroimaging studies have shown white-matter abnormalities in the corpus callosum and limbic network (*8*) along with grey-matter reductions throughout the cortex, most consistently in the medial temporal lobes (*9,10*). While these correlates provide valuable information about potential biomarkers, correlative neuroimaging is inherently limited in its capacity to provide causal information as observed abnormalities could be compensatory responses, spurious correlations, or pleiotropic genetic effects (*9,11*).

Causal mechanisms of disease are often established in animal models, but animal models of schizophrenia cannot comprehensively reflect symptoms of human schizophrenia (*12*). Given these limitations, mechanistic insights may be gleaned from human diseases that cause schizophrenia-like symptoms. For instance, some N-methyl-D-aspartate (NMDA) antagonist drugs and anti-NMDA receptor encephalitis cause symptoms closely resembling schizophrenia

(*13,14*). Psychotic symptoms can also be induced by dopaminergic drugs and alleviated by dopamine receptor antagonists. While modulation of NMDA and dopamine receptors provides causal information, these receptors are widely distributed throughout the brain so offer limited evidence of the specific anatomy involved in schizophrenia-like symptoms.

These limitations highlight the value of cases of new-onset psychosis acutely following a focal brain lesion, as these cases can link specific anatomy with the cause of psychosis (*15*). Lesions that cause psychosis, however, do not always occur in the same brain region (*16*). A possible explanation for the regional heterogeneity is that the unit responsible for psychosis is not a single brain region, but connections between multiple brain regions. This hypothesis can be investigated using a normative brain functional connectome to determine if lesions in disparate locations across the brain affect a common circuit of functional connections (*17*). This technique, known as lesion-network mapping, has previously been used to establish a model of familiarity detection by mapping the functional connectivity of lesions that cause isolated delusions of misidentification (*18*). This study successfully identified regions specific to familiarity, but specifically excluded other types of delusions, such as persecutory delusions which are more common in schizophrenia. A second study identified a common circuit for lesions that cause hallucinations across sensory modalities (visual, auditory, olfactory, tactile) (*19*). Olfactory and tactile hallucinations are rare in schizophrenia, and most (78/89) cases from this study presented with no other psychotic symptoms and therefore would not meet symptom criteria for schizophrenia. Thus, while both studies investigated important anatomy for isolated symptoms and general hallucinations, neither attempted to model schizophrenia.

Here, we investigate lesions causing symptoms that mimic schizophrenia, a syndrome defined by a constellation of multiple psychotic symptoms including hallucinations, persecutory delusions, and disorganized thought. We derived and cross-validated a circuit based on the functional connectivity of published cases of lesion-induced psychosis, with a focus on cases described by clinicians as “schizophrenia” or “schizophrenia-like”. As lesion network mapping has previously identified effective brain stimulation targets across multiple neuropsychiatric disorders (*17, 20-23*), we perform an exploratory analysis using a lesion-derived circuit to identify a novel target for future TMS studies in schizophrenia.

RESULTS

Case Selection

Following PRISMA guidelines, we conducted a systematic review of PubMed for lesions that cause psychotic symptoms. We identified 155 cases of lesions that caused at least one psychotic symptom (Figure S1). Among these cases, 85 individuals developed visual hallucinations, 81 auditory hallucinations, 63 delusions, 25 thought disorder (cases were included in the category of ‘thought disorder’ if the subject’s speech was described as “incoherent”, “disorganized”, or “flight-of-ideas”). All individuals with delusions had at least one delusion that could be described as paranoid. 83 cases presented with more than one symptom. 41 reports used the terms "schizophrenia" or "schizophrenia-like" to describe the symptoms caused by the lesion.

Lesion Location Mapping

Each lesion was manually traced onto a common template in MNI space (Figure S2). Lesions that caused psychosis were distributed heterogeneously throughout the brain. Lesion locations were not overrepresented in any specific vascular territory or lobe of the brain (Figure S3).

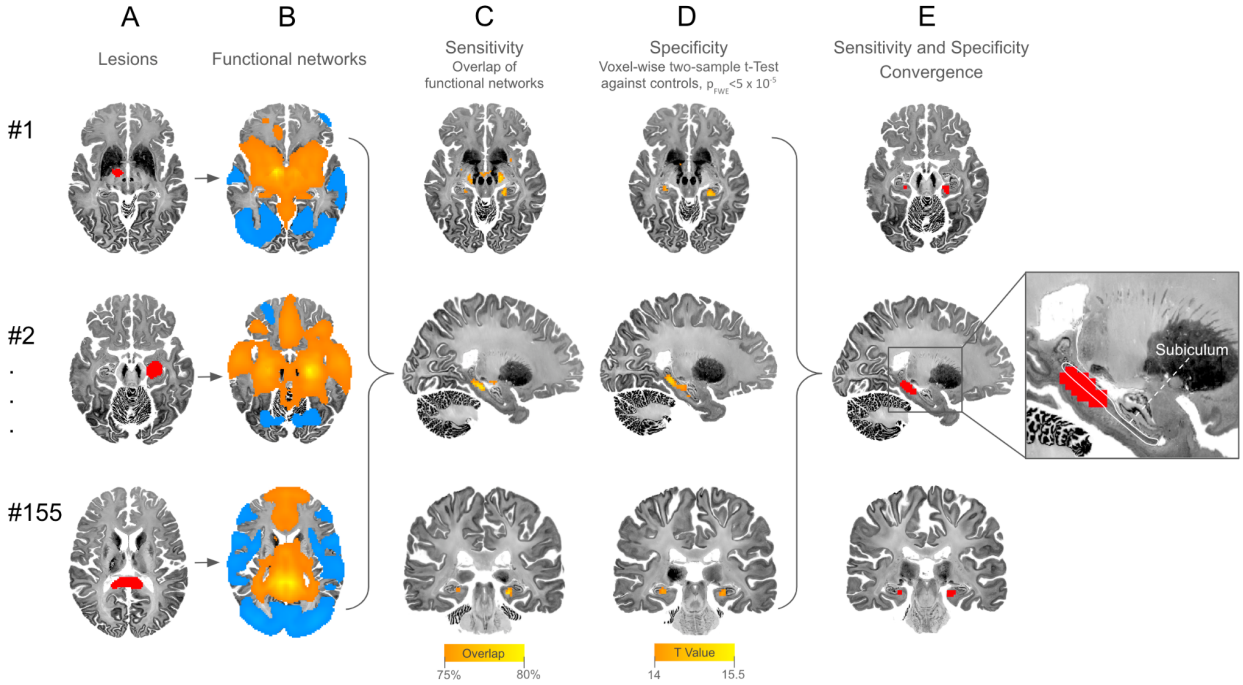
Lesion Network Mapping

The functional connectivity of each lesion was estimated by correlating the lesion location with a normative functional connectome derived from healthy young adult subjects (n=1000) (*24*) (Figure 1A,B). A sensitivity analysis found that over 75% (116/155) of the lesions' functional-connectivity maps overlapped the posterior subiculum of the hippocampus, with each map thresholded at $|T|>7$ as in prior work (*18,19,22,25*) (Figure 1C). These results were unchanged when using T-value thresholds of 5 and 10 (spatial $r>0.99$, peak remained in the subiculum). To avoid bias from arbitrary thresholding, we also conducted a one-sample t-test at each voxel to identify regions consistently present in the unthresholded connectivity maps of psychosis-inducing lesions. This peak remained in the posterior subiculum ($p_{FWE}<5x10^{-4}$) (*26,27*), suggesting that lesions that cause psychosis have common functional connectivity to this region.

To assess specificity, we compared the connectivity maps of lesions that caused psychosis with a control groups of lesions not associated with psychosis (control group composed of n=490 stroke patients who presented consecutively to the Massachusetts General Hospital and n=947 published cases of lesions not associated with psychosis) using a two-sample t-test with FWE correction at each voxel, which again yielded a peak in the posterior subiculum ($p_{FWE}<5 \times 10^{-5}$) (Figure 1D). This result was driven by the experimental group rather than the control group, as the peak voxel in the subiculum (MNI [24,-24,-16], T=15.5) from this two-sample t-test was not strongly represented in one-sample t-tests of the control group (T=0.6). Results were highly similar when comparing lesions that caused psychosis with each set of controls separately (r=0.90)(Figure S4).

To determine the most sensitive and specific region of this psychosis circuit, the sensitivity and specificity maps were combined into an overall conjunction map (Figure 1E). The primary peak remained in the posterior subiculum. Secondary peak regions that emerge at slightly lower thresholds for sensitivity (overlap >70%) and specificity ($p_{FWE}<5x10^{-4}$) were the ventral tegmental area, mediodorsal and midline thalamic nuclei, retrosplenial cortex, and lobule IX and dentate nucleus of the cerebellum (Figure S5).

Figure 1
Lesions that Cause Psychosis Map to a Common Circuit of Functional Connectivity

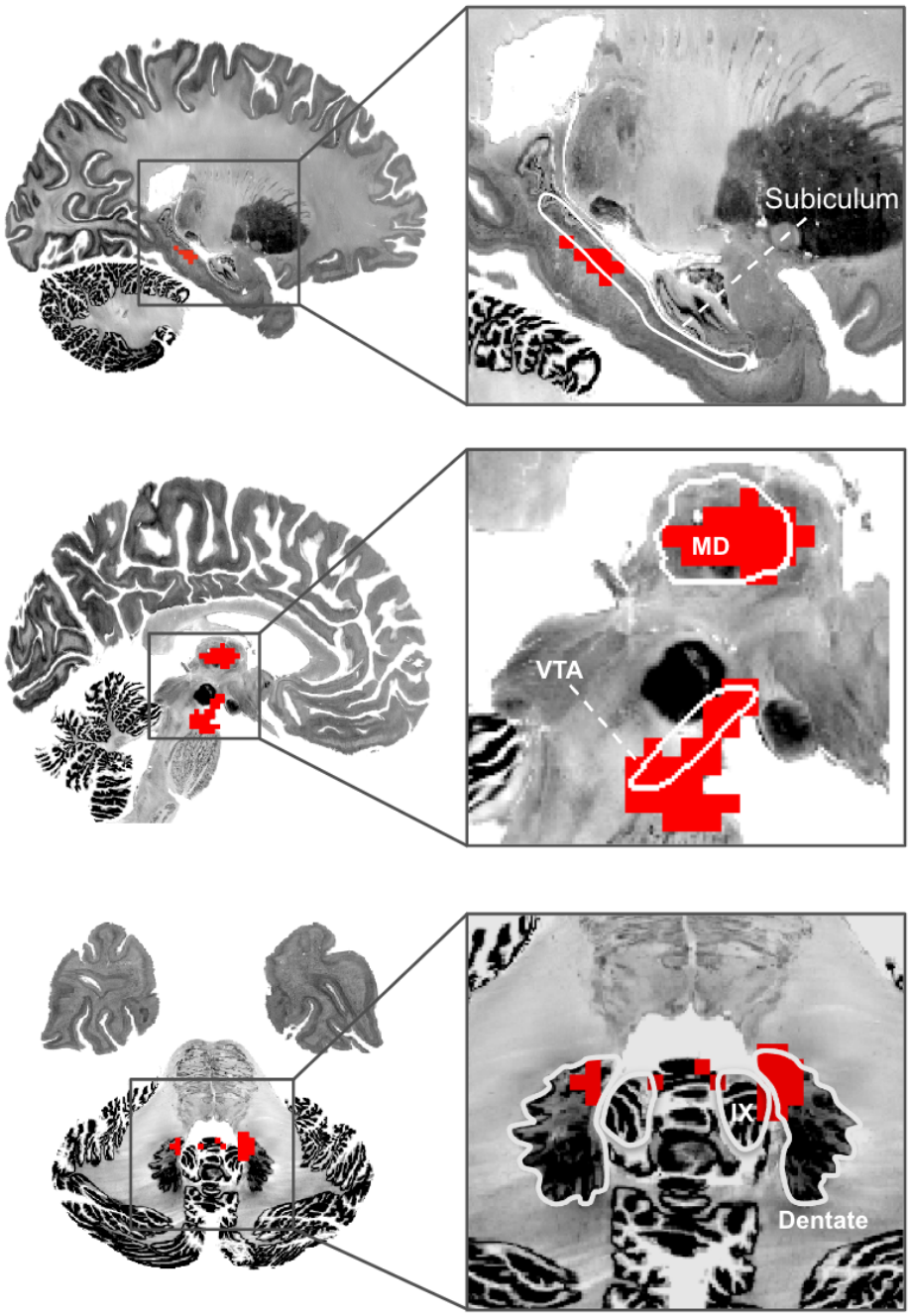


(a) Each lesion traced manually onto a standard brain atlas (*28*). **(b)** Normative connectivity of each lesion was determined using a normative connectome database (n=1000) (*24*). **(c)** Sensitivity analysis showing the overlap of functional connectivity of >75% of lesions, thresholded at |T|>7. **(d)** Specificity analysis showing the results of a two-sample t-test ($p_{FWE}<5 \times 10^{-5}$) comparing functional connectivity of lesions that cause psychosis and control lesions. **(e)** Convergence map depicting the posterior subiculum as the most sensitive and specific region affected by lesions that cause psychosis. Subiculum is defined by the CoBrALab Merged Atlas (*29*).

Next, we tested whether results from this analysis were driven by a circuit effect or by hippocampal lesions alone. 52 of the lesions that caused psychosis included at least one voxel in the hippocampus or amygdala. We excluded these 52 lesions and repeated the sensitivity and specificity tests on the 103 lesions that did not intersect the hippocampus or amygdala. This analysis yielded equal peaks (>75% overlap, $p_{FWE}<5x10^{-5}$) in the posterior subiculum of the hippocampus, the ventral tegmental area, mediodorsal and midline nuclei of the thalamus, and lobule IX and dentate gyrus of the cerebellum (Figure 2). The specificity map from this analysis was nearly identical to its counterpart that included hippocampal and amygdalar lesions (spatial r=0.98). These results suggest that symptoms of psychosis were caused by lesions with functional connectivity to the posterior subiculum, not just by lesions that intersect the hippocampus.

To determine the similarity between the functional connectivity profiles of each individual lesion and the overall specificity map, we performed a leave-one-out cross-validation. A spatial correlation was computed between the functional connectivity profile of each individual lesion (Figure S6a) and a specificity map generated from the remaining 154 lesions (Figure S6b). The overall functional connectivity profile was similar between lesions that cause psychotic symptoms (one-sample t-test: $p=8.5x10^{-21}$).

Figure 2
Common functional connectivity analysis excluding hippocampal lesions



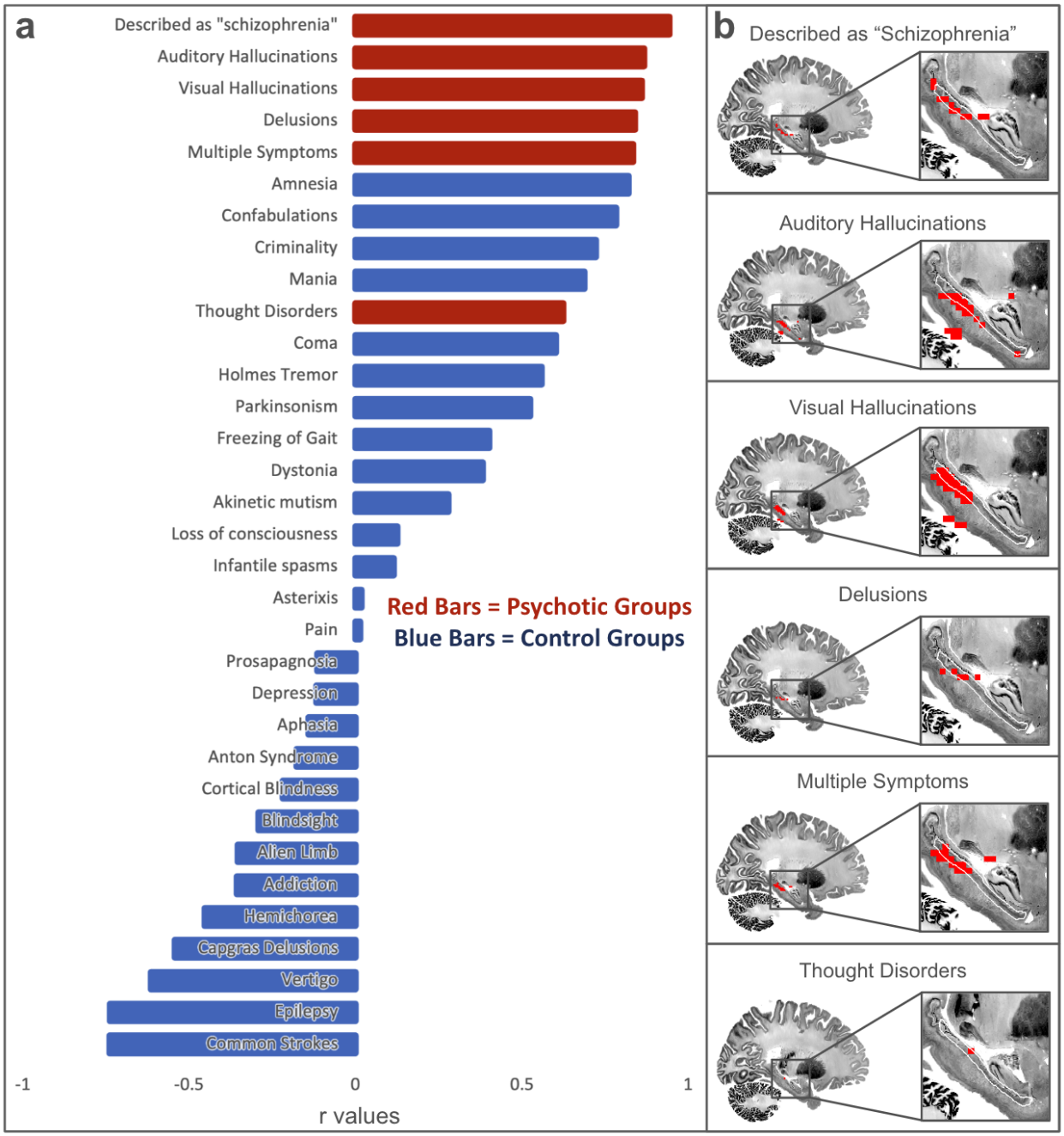
Convergence map depicting regions that are sensitive (overlap of functional connectivity of >70%) and specific (voxel-wise two-sample t-test against controls, $p_{FWE}<5 \times 10^{-5}$) to a circuit affected by lesions that cause psychosis and do not directly intersect the hippocampus or amygdala (n=103). MD=Mediodorsal Nucleus of the Thalamus; VTA=Ventral Tegmental Area. Dentate=Dentate Nucleus of the cerebellum; IX=Lobule IX of the cerebellum

Different symptoms of psychosis map to a similar circuit

To determine if different psychotic symptoms mapped to similar anatomy, we categorized lesions into symptom groups —delusions, thought disorders, visual hallucinations, and auditory hallucinations—based on the corresponding symptom(s) each lesion induced. Identical to the method in Figure 1d, we derived a specificity map for each symptom group by comparing that symptom group to control symptoms in a voxel-wise two-sample t-test. We then used spatial correlations to compare the specificity map of each symptom group with a specificity map generated from the remaining psychotic symptom groups, effectively constituting a leave-one-symptom-out analysis. For comparators, we repeated this analysis for each symptom group within the control group (Figure 3a). Most of the resulting maps of psychotic symptoms were highly similar to maps for other psychotic symptoms (median spatial r=0.84, range 0.62-0.94) and displayed a similar peak in the subiculum (Figure 3b). One exception was the specificity map for thought disorder, which was less similar to other lesions that caused psychotic symptoms (r=0.62) and had a primary peak in the corpus callosum with a secondary peak in the subiculum. This exception may be partially explained by the relatively small sample size (n=25) of the thought disorder group.

These results suggest that lesions that cause different symptoms of psychosis have functional connectivity profiles that are more similar to each other than to controls.

Figure 3
Functional connections of lesions that cause different symptoms of psychosis share a common functional connection to the posterior subiculum of the hippocampus, and are more correlated with each other than with lesions that cause other symptoms



a) Correlation values of unthresholded functional connectivity between psychosis circuit and different symptom groups. Lesions from each symptom group were excluded from the psychosis circuit when they were correlated to avoid autocorrelation **b)** Each grouping of psychotic symptoms had peak sensitivity (overlap >75%) and specificity ($p_{FWE}<5 \times 10^{-4}$) in the posterior subiculum of the hippocampus (outlined in white).

To further test the hypothesis that lesions that caused different symptoms of psychosis were more similar to each other than to controls, we used spatial correlations to compare the functional maps of each symptom group (Figure S7a) to two different comparator groups: one comprised of lesions causing psychosis without the symptom group under examination, and the other comprised of control lesions that did not cause psychosis (Figure S7b). The functional connectivity of lesions that caused each psychotic symptom was more similar to other psychosis-inducing lesions than to lesions that did not cause psychosis (Figure S7c).

From this analysis we conclude that different psychotic symptoms converge on a common network. The posterior subiculum was not specific to any particular symptom of psychosis, but may rather be a common functional connection of schizophrenia-like symptoms.

Although the previous analysis is in concordance with our primary hypothesis — that lesions causing a schizophrenia-like syndrome map to a similar functional connectivity profile — these results do not exclude the possibility that there are subtle differences in lesion network localization between different symptoms. In an exploratory analysis, we compared each symptom-specific grouping with the remaining psychosis-inducing lesions using a voxel-wise partial correlation, controlling for co-occurring symptoms in each case. In most cases, the functional maps of lesions that caused each group of psychotic symptoms did not significantly differ from the functional maps of lesions that caused other psychotic symptoms. The exception was lesions that caused thought disorder (n=25), which were significantly more positively correlated to the fornix, body of the corpus callosum, and a cluster of voxels extending from the anterior corona radiata to the inferior frontal gyrus bilaterally (Figure S8). Notably, lesions that caused symptoms described as “schizophrenia” or “schizophrenia-like” did not significantly

differ from other cases of lesions that caused psychotic symptoms, indicating that these two groupings shared similar functional connectivity profiles. These results suggest that lesions causing multiple psychotic symptoms have a common functional connectivity profile.

Distinctions between different symptoms of psychosis in isolation

The above analyses examined psychotic symptoms when they occur together, but in some cases individual psychotic symptoms occurred in isolation. One may expect that auditory or visual hallucinations in isolation would localize to their respective primary sensory areas. To explore this possibility, we examined the lesions within our cohort that caused symptoms in isolation. 35 lesions caused isolated visual hallucinations, 24 caused isolated auditory hallucinations, and 8 caused isolated paranoid delusions. As above (Figure 1), we computed the functional connectivity of each of these lesions and performed a sensitivity test by calculating the highest percentage of functional connection overlap at a threshold $|T|>7$, and a specificity test by comparing each isolated symptom cohort with control lesions using a voxel-wise two-sample t-test. In addition to FWE correction for comparisons across voxels, we used False Discovery Rate correction to account for comparative analysis across the symptom groupings.

Lesions that cause isolated visual hallucinations again localized to the subiculum (>90% overlap, $p_{FWE}<5x10^{-4}$) (Figure S9); however, it is notable that lesions causing isolated visual hallucinations by disrupting primary visual input (Charles-Bonnet Syndrome) were excluded from this study as this symptomology is not seen in schizophrenia.

Lesions that cause isolated auditory hallucinations still had peak overlap in the subiculum (86%

overlap, $p_{FWE}<0.05$), but the most specific region was in the subcortical auditory system (46% overlap, $p_{FWE}<.0003$). Lesions that caused isolated auditory hallucinations were exclusively located in either the temporal lobe (n=13, seven of which intersected Heschl's Gyrus) or brain stem (n=11). Temporal lesions causing isolated auditory hallucinations had peak connectivity to the superior temporal gyrus (85% overlap, $p_{FWE}<5x10^{-5}$) (Figure S9). Brainstem lesions causing isolated auditory hallucinations had peak connectivity to the subcortical auditory system (100% overlap, $p_{FWE}<5x10^{-5}$) (Figure S9). Of note, no patients with isolated auditory hallucinations had symptoms that were described as "schizophrenia" or "schizophrenia-like". Six of these cases had isolated auditory hallucinations of simple repetitive sounds (e.g. "rain falling on the roof" or "a machine humming"), 14 had hallucinations of familiar music, and four had both familiar music and simple sounds. These hallucinations did not include distinguishable language, and all patients retained insight that the hallucinations were not real.

Lesions that caused isolated persecutory delusions localized to the right mediodorsal thalamus (100% overlap, $p_{FWE}<0.05$) (Figure S9).

Distinguishing lesions that cause psychosis from lesions that cause amnesia

The results from these analyses identified the hippocampus and retrosplenial cortex as sensitive and specific functional connections to lesions that cause psychosis. These regions have long been known to be involved in memory, and have previously been implicated in a memory circuit derived from 53 lesions that cause amnesia (*25*). In addition, the functional connections of lesions that cause psychosis were more similar to the functional connections of lesions that cause

amnesia than any other control group (spatial r=0.82) (Figure 3A). Yet, amnesia is not always accompanied by psychotic symptoms, raising the question of how these two circuits may differ.

Among the 53 published amnesia cases, six (11%) also had symptoms of psychosis (one had visual hallucinations, one had auditory hallucinations, one had delusions, two had thought disorder, one had visual hallucinations and delusions). Among the 155 psychosis cases in this study, 42 reported an acute memory deficit, 7 reported no memory deficit, and 106 did not report any memory testing.

To evaluate specificity between psychosis and amnesia, we first compared the functional connections between lesions causing psychosis (n=155) and lesions causing amnesia without psychosis (n=47) using a voxel-wise two-sample t-test. Lesions causing psychosis were more functionally connected to aspects of the middle temporal gyrus, and lesions causing amnesia were more functionally connected to the retrosplenial cortex, anterior nuclei of the thalamus, fornix, and medial prefrontal cortex ($p_{FWE} < 0.05$). To directly contrast psychosis and amnesia, we then compared the functional connections of lesions that caused both psychosis and amnesia (n=42) to lesions causing amnesia without psychosis (n=47). Lesions causing psychosis were more functionally connected to aspects of the superior temporal gyrus, the ventral claustrum, and part of the uncinate fasciculus ($p_{FWE} < 0.05$) (Figure S10). Lesions causing amnesia without psychosis were not associated with any significant voxels in this comparison.

Seven cases reported psychosis with documented absence of amnesia. These cases showed 100% overlap of functional connectivity (thresholded at T>7) in the hippocampus, overlapping

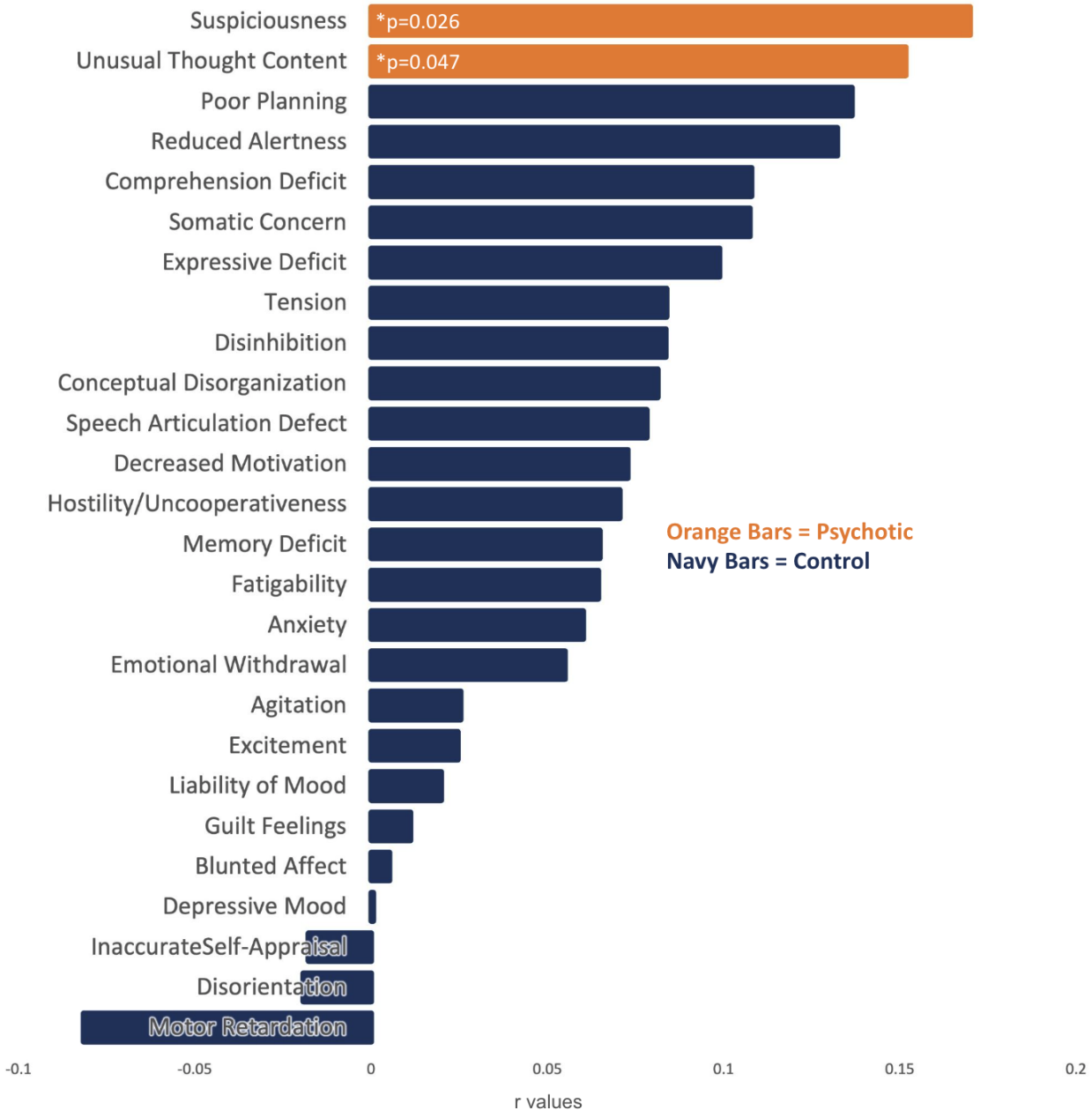
predominantly with posterior subiculum. However, none of these voxels survived multiple comparisons correction. Due to variable memory testing, these two cohorts remain a coarse distinction between amnesia and psychosis.

To explore laterality effects, we categorized all lesions by hemisphere. Lesions causing psychosis were more likely to involve the right hemisphere while lesions causing amnesia were more likely to involve the left hemisphere (psychosis: n=7:18:16 (Left:Bilateral:Right) vs. amnesia: 17:21:8; (χ^2 p=0.01).

Validation in an independent lesion dataset

Next, we tested the lesion-derived psychosis circuit in an independent cohort of 181 patients who completed the clinician-rated neurobehavioral rating scale (NBRS)(*30*) in the Vietnam Head Injury Study (VHIS)(*31*). This study included male American military Veterans (mean age 58.4 ± 3.1) who suffered penetrating head trauma during the Vietnam War. We hypothesized that our psychosis circuit would be preferentially connected to lesions that induce psychosis-like symptoms in this dataset - i.e. “suspiciousness” and “unusual thought content” - relative to 24 control symptoms unrelated to psychosis. In line with our hypothesis, lesions with greater connectivity to the psychosis circuit were more likely to be associated with suspiciousness and unusual thought content (p=0.025 and 0.046, respectively) (Figure 4) than the other 24 control symptoms.

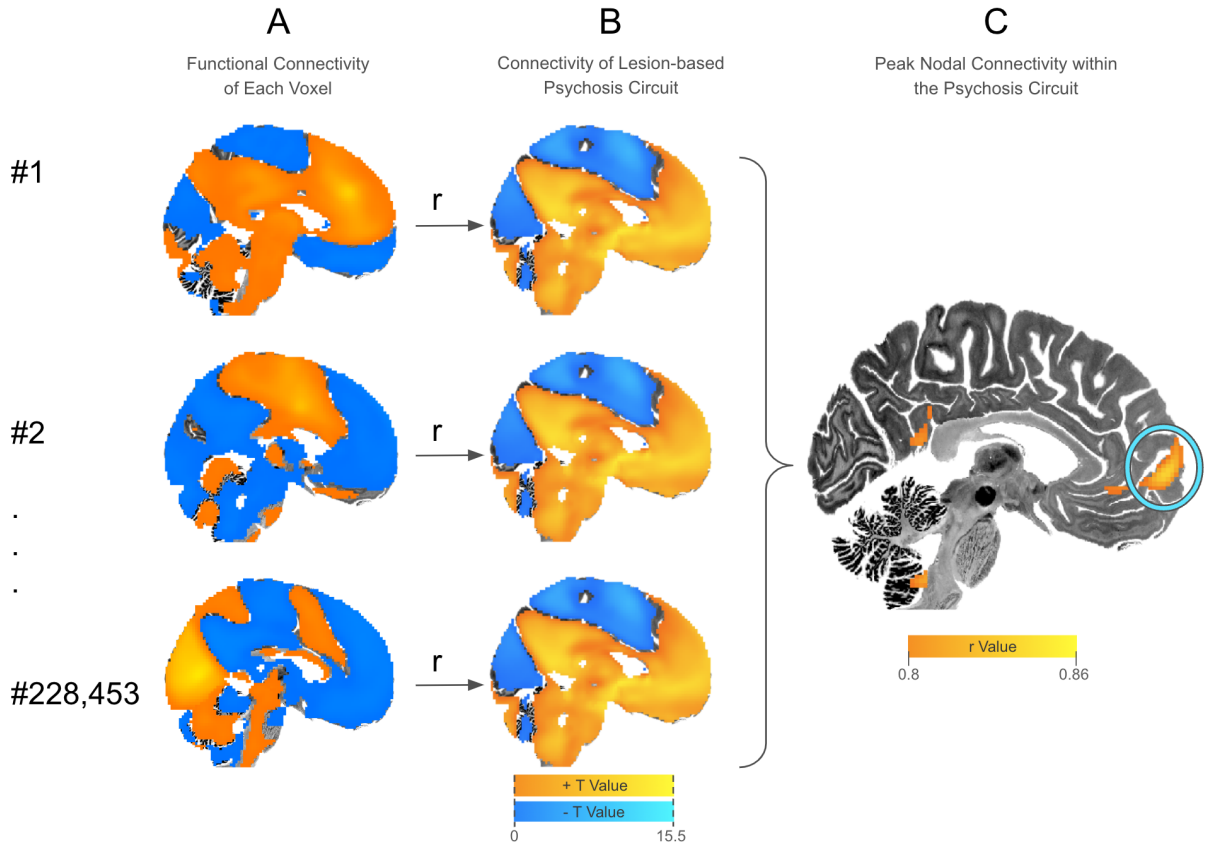
Figure 4
Correlation values between functional maps of lesions causing psychosis and lesions causing specific symptoms from an independent cohort.



Determination of potential target

Finally, we determined a potential TMS target whose intrinsic functional connectivity most closely resembles the psychosis circuit derived here. Using a normative connectome database (n=1000), we estimated the whole-brain connectivity of each voxel in the brain (Figure 5a). We then used spatial correlations to compare the connectivity map of each voxel with the psychosis specificity map (Figure 5b). This produced a map denoting voxels expected to target the psychosis circuit as specifically as possible (Figure 5c). As expected, the peak correlation in this analysis was in the subiculum (r=0.83), but this location is too deep to access with TMS. A specific site within the right rostromedial prefrontal cortex (rmPFC) (MNI [2,66,2]) was both highly correlated to the psychosis circuit (r=0.82) and sufficiently superficial to serve as a target for TMS (Figure 5c, circled in blue).

Figure 5
Therapeutic TMS target determined by correlation with each voxel's intrinsic functional connectivity.



a) BOLD correlations for each voxel in a 2mm brain template **b)** correlated with unthresholded BOLD correlation for the two-sample t-test between lesions causing psychosis and controls **c)** determining voxels with strongest correlation between intrinsic resting-state BOLD signal and BOLD signal specific to lesions that cause psychosis. TMS target circled in blue.

DISCUSSION

The findings from this study indicate that lesions that cause psychotic symptoms map to a common circuit of functional connectivity to the posterior subiculum of the hippocampus. Analysing different psychotic symptoms and excluding of hippocampal lesions both reproduced a similar psychosis circuit. This circuit was associated with psychotic symptoms in an independent cohort. A region in the rmPFC is a promising target to modulate this circuit with TMS. There are several important implications to these findings.

First, we provide evidence that disruption of a specific circuit can cause psychosis. The anatomy of this circuit is consistent with correlative neuroimaging findings of hippocampal involvement in psychosis. In patients with schizophrenia, the hippocampus has shown abnormal metabolic activity on PET (*32*), increases in cerebral blood volume (*33*), reduced posterior and increased anterior activation on fMRI (*34*), and reduced volume on structural MRI (*9,35*). However, these correlative findings are unable to fully address confounders, thus leaving uncertainty whether hippocampal changes are directly causal, spurious, or compensatory (*15*). Anti-NMDA-receptor encephalitis and some NMDA receptor antagonists have been hypothesized to cause schizophrenia-like symptoms via their effect on the hippocampus (*36–38*), but these conditions affect receptors widely distributed throughout the brain. Our results are derived from spatially-confined lesions that cause psychosis, therefore providing evidence that a brain circuit defined by hippocampal connectivity is causal of psychotic symptoms. Critically, this was driven by a circuit-level effect and not by hippocampal lesions alone, as a similar circuit was derived even when excluding lesions that touch the hippocampus.

The essential region of this circuit is in the posterior subiculum of the hippocampus. The subiculum is the primary outflow tract of hippocampus to the fornix (*39,40*), from which the hippocampus communicates with subcortical structures such as the mamillary bodies, septal nuclei, and anterior nuclei of the thalamus (*40–42*). The subiculum has afferent and efferent connections with CA1 (*43,44*), the retrosplenial (*45–47*) and rhinal cortices (*48,49*), and afferent projections to the medial prefrontal cortex (*50,51*). Its role in psychosis may involve aberrancy in assimilation of hippocampal input or dissemination of processed information across diverse neural pathways. This is consistent with recent studies showing that, as the disease of schizophrenia progresses, grey matter atrophy spreads to regions structurally or functionally connected to the hippocampus (*52,53*). Other studies have shown that increased metabolism in CA1 in patients at high risk for psychosis progresses to the subiculum if they have a psychotic episode (*54*).

Posterior subicular dysfunction could explain how psychotic symptoms manifest as a syndrome. While isolated psychotic symptoms can result from the distortion of a single primary sensory input, schizophrenia affects multiple sensory modalities. This suggests that symptoms of schizophrenia result as a downstream effect of higher-order dysfunction (*55*). Hippocampal outflow may be involved in navigating our conceptual and symbolic environment (*56–58*), and the posterior hippocampus has been proposed to be responsible for contextualizing sensory information in memory and anchoring memory in sensory reality (*59*). The posterior subiculum may therefore serve as a critical conduit between bottom-up and top-down processing involved in reality monitoring. Anomalous communication from this region could produce delusions and

hallucinations by misrepresenting internal thoughts as external sensory reality or corrupting external sensory input with unrealistic internal representations.

We also identified several secondary peak regions in the psychosis circuit: the mediodorsal and midline nuclei of the thalamus, the VTA, and retrosplenial cortex. All of these regions have robust white matter connections with the hippocampus (*40,45,46,60–65*). Our results also implicate lobule IX and the dentate nucleus of the cerebellum, which are not directly connected to the hippocampus. Lobule IX has been associated with language, social, and emotional task performance (*66*) and is a principal region of cerebellar grey matter loss in patients with schizophrenia (*67*). The dentate nucleus has been implicated in previous lesion-network-mapping studies of auditory hallucinations (*19*). It is notably the only cerebellar output known to affect the prefrontal cortex and does so in part through projections to the mediodorsal nucleus of the thalamus (*68*).

The involvement of the VTA in this psychosis circuit is consistent with the established dopamine hypothesis of schizophrenia — i.e dopaminergic agonists can cause psychosis, while dopaminergic antagonists are first-line treatment for schizophrenia. Dopaminergic connections are widespread throughout the brain and could account for coordination of disparate brain regions. In addition to the VTA, several regions in this psychosis circuit are involved in dopamineric communication. Notably, the subiculum's capacity to modulate dopaminergic neurons in the VTA (*69*) is hypothesized to explain pathologically increased salience in patients with schizophrenia (*70*). Further, the mediodorsal nucleus highly expresses dopamine receptors (*71,72*) and the dentate nucleus has a role in regulating dopaminergic neurotransmission (*73*).

The anatomical similarity of the psychosis and memory circuits raises the question of why apparently similar lesions can cause psychosis in some patients but amnesia in others. Memory deficits are a known complication of schizophrenia (*74*), but psychosis does not always accompany memory deficits. Lesions that cause psychosis were more likely to have functional connections to the temporal gyri, though more detailed symptoms for each case would likely improve anatomical distinction. Lesions that cause psychosis were also more likely to be restricted to the right hemisphere, consistent with literature reporting the development of psychotic symptoms from right-sided lesions in stroke patients16 and right-sided hippocampal damage in patients with traumatic brain injury (*75*) and Alzheimer's disease (*76*).

Beyond amnesia, distinct symptoms of psychosis mapped to similar circuits, as did the functional maps of lesions that caused "schizophrenia" or "schizophrenia-like" symptoms. This supports the premise that this lesion-derived psychosis circuit is causally linked with symptoms that approximate primary schizophrenia. It also supports the conceptualization of schizophrenia as a unified syndrome with discrete anatomy affected, rather than a constellation of symptoms that arises from multiple coincidental insults.

Across the whole brain, the intrinsic connectivity of the right rmPFC was highly correlated with the lesion-derived psychosis circuit. Prior work has shown that lesion-derived circuits can reveal TMS targets for addiction, depression, and pain (*20,22,77*). This suggests that modulating the rmPFC with TMS may modulate the lesion-based circuit described here. As lesions presumably

disrupt communication between regions, we hypothesize that TMS targeted to the right rmPFC performed with parameters to increase activity (*78*) could reduce symptoms of psychosis. A similar target in the rmPFC has previously been proposed based on abnormal fMRI activation in this region when patients with schizophrenia perform a reality-monitoring task (*79*); furthermore, healthy controls have shown improvement on a reality-monitoring task after receiving rTMS to this target (*80*). However, rmPFC has not been used as a target in patients with schizophrenia. Trials of other TMS targets for schizophrenia have suggested that the treatment is broadly safe (*81*), but it is not yet used in clinical practice because the optimal approach remains unclear. Thus, we propose the rmPFC as a target for prospective TMS trials to ameliorate symptoms of psychosis.

Strengths of this study include large sample size, causal localization, rigorous permutation-based statistics, validation in an independent dataset, and an agnostic, data-driven approach that produced findings consistent with preexisting literature on the hippocampus and psychosis. There are also several limitations. First, the data used in this study are not from patients with primary schizophrenia. Causality can be difficult to study in primary schizophrenia given genetic and environmental influences on the disease. Future studies may be able to generalize causality of this lesion-derived circuit to primary schizophrenia if modulation of this circuit correlates with a therapeutic response, or if our causal neuroanatomy aligns with expression of genes known to be involved in schizophrenia. Second, lesions functionally connected to the posterior subiculum do not always cause psychosis, implying involvement of other mechanisms such as genetic susceptibility, circuit-level compensation, or communication between different neuronal subpopulations. Relatedly, the methods used in this study cannot characterize how lesions that

caused psychosis altered communication with the subiculum. The subiculum contains a diverse group of cells and outputs (*82*), and the complexity of these regional interactions is simplified here to correspond with the limitations in spatial specificity of neuroimaging. Future studies are needed to more finely characterize the communication between these regions. Third, despite a relatively large sample size, it is possible that the study was not adequately powered to detect all regions involved in psychosis or to detect differences between psychotic symptoms. Our analysis was based on published case reports, which are valuable in lesion network mapping because they report a stark change that temporally coincides with the lesion. However, future studies could expand the sample size by extracting electronic medical record data on lesion-induced psychosis. Finally, a prospective trial would be necessary before the rmPFC TMS target described in this manuscript can be recommended clinically.

Despite these limitations, our results demonstrate the existence of a distinct brain circuit that is causally implicated in symptoms of psychosis, particularly in cases that resemble schizophrenia. The essential region of this circuit is in the posterior subiculum of the hippocampus.

MATERIALS AND METHODS

Study Design - Case Selection

We identified published cases of brain lesions associated with psychosis with a systematic search on PubMed according to PRISMA Guidelines (Figure S1) (*83*). We excluded cases with a prior history of psychosis. Cases were included only if there was evidence of a clear temporal relationship between the lesion and the psychotic symptoms (the lesion was determined to be acute on imaging, the patient had negative imaging within the past year before the psychotic symptoms started, or resolution of the lesion coincided with symptom resolution). Symptoms of schizophrenia are commonly split into 'positive' symptoms (delusions, thought disorders, hallucinations) and 'negative' symptoms (apathy, avolition, cognitive deficits). Negative symptoms were excluded from the analysis as isolated negative symptoms are not specific to schizophrenia. Cases of Charles-Bonnet syndrome, or visual-release hallucinations that occur as a complication of acquired visual field defects and occur exclusively in the blind field of vision, were excluded because these types of hallucinations are not seen in schizophrenia.

Study Design - Lesion Network Mapping

Lesions were reconstructed by manually tracing the published images of the lesions onto a common MNI template using 3D Slicer (Boston, MA; https://www.slicer.org/) (*84*). Although published cases are limited in providing only 2-dimensional images of the lesions, prior work had demonstrated that this approximation is sufficient for lesion network mapping (*18*). The functional connectivity of each lesion location was estimated using a normative database of resting-state functional connectivity (n=1000) (*24*), generating a brain-wide map of correlation values for each lesion. We derived maps of brain-wide t values for each lesion by performing a

one-sample t-test on the Fisher transformed correlation values derived from the previous step. These analyses were repeated and validated using a separate normative database (n=1,570) (*85*). The normative connectome data were preprocessed as previously described (*24, 85*). All statistical tests were performed using MATLAB R2022b except as otherwise specified.

Lesion Network Mapping - sensitivity analysis

To investigate sensitivity, we first set a threshold of $|T| \geq 7$ to the normative functional connectivity maps of lesions that caused psychosis. This threshold approximately corresponds to Bonferroni-corrected $p < 5 \times 10^{-6}$ and is consistent with prior LNM studies (*27*). We then identified voxels functionally connected to the greatest percentage of lesions that caused psychosis. We repeated the analysis at T-value thresholds of 5 and 10 to ensure the results were not threshold-dependent.

To ensure that results were not driven by arbitrary thresholds, we performed a one-sample t-test on the unthresholded functional connectivity maps of all the lesions that caused psychosis, and used the Westfall-Young procedure to correct for multiple comparisons. The voxels that survived this correction served as a mask for the percentage-overlap sensitivity test.

Lesion Network Mapping - specificity analysis

We evaluated the specificity of our findings by comparing the connectivity maps of lesions that caused psychosis with two independent control groups: lesions of consecutive stroke patients presenting to Massachusetts General Hospital (n=490) (*86*), and lesions in our group's database that caused symptoms not related to psychosis (n=947, including Addiction, Akinetic Mutism, Alien Limb syndrome, Amnesia, Anton syndrome, Asterixis, Blindsight, Coma,

Confabulations, Cortical blindness, Criminality, Capgras Delusions, Depression, Dystonia, Epilepsy, Freezing of Gait, Hemichorea, Holmes Tremor, Infantile Spasms, Loss of Consciousness, Mania, Pain, Parkinsonism, Prosopagnosia, and Vertigo).

We performed two-sample t-tests at each voxel between the cases and combined controls group (n=1437). We used the permutation-based FWE correction in FSL PALM (*87*) to correct for multiple comparisons, following the Westfall-Young procedure.

Lesion Network Mapping - conjunction

We binarized the sensitivity map according to whether a voxel was connected to at least 75% of lesions causing psychosis at a threshold of $|T| \geq 7$ and also survived the FWE-corrected one-sample t-test. We also binarized the results of the specificity analysis according to whether a voxel survived FWE correction. We overlaid these binarized maps and consider voxels that were commonly nonzero in both maps to be sensitive and specific.

Analysis without hippocampal lesions

We repeated the above analysis after removing any lesions that had voxels in the hippocampus as defined by the Brainnetome atlas (*88*). In the cohort of lesions that did not touch the hippocampus, we then repeated the above analyses. For the sensitivity portion, we calculated which voxels had overlapping functional connections of >70% of non-hippocampal lesions at a threshold of $|T| \geq 7$. We then overlaid an FWE-corrected one-sample t-test of the functional maps of non-hippocampal lesions, and only included voxels that passed both tests in our sensitivity result. For the specificity test, we compared the functional maps of non-hippocampal lesions that caused psychosis with the same control group described above.

Similarity between different symptoms of psychosis

We first categorized cases into four classes of positive symptoms of psychosis: delusions, thought disorder, visual hallucinations, and auditory hallucinations. If a case had more than one symptom, they were included in multiple symptom groups. We made separate groups for subjects that had only one symptom in isolation.

We derived a specificity map for each symptom of psychosis and for each subgroup within the control group (Consecutive incidental strokes, Addiction, Akinetic Mutism, Alien Limb syndrome, Amnesia, Anton syndrome, Asterixis, Blindsight, Coma, Confabulations, Cortical blindness, Criminality, Capgras Delusions, Depression, Dystonia, Epilepsy, Freezing of Gait, Hemichorea, Holmes Tremor, Infantile Spasms, Loss of Consciousness, Mania, Pain, Parkinsonism, Prosopagnosia, and Vertigo). We performed a voxel-wise two-sample t-test between the symptom group and all the lesions that were not part of their symptom group. We then performed spatial correlations between each of these symptom groups and the general psychosis circuit, excluding, lesions from the psychotic symptom group being examined. We then performed a LNM analysis on each of the psychotic symptom groups, with thresholds of >75% overlap of functional connections for the sensitivity test and $p_{FWE}<5 \times 10^{-4}$ for the voxel-wise two-sample t-test against controls for the specificity test.

We then correlated the functional map of each lesion causing a specific symptom of psychosis with a one-sample t-test of control lesions and a one-sample t-test of psychosis lesions, excluding the symptom under examination. To determine if lesions that caused a specific symptom of

psychosis had functional connections more similar to controls or to other lesions causing psychosis, we performed a two-sample t-test between the distributions of correlations with controls and the distributions of correlations with other psychosis lesions.

Distinctions between different symptoms of psychosis presenting as a psychotic syndrome

To determine if different symptoms of psychosis correspond to distinct functional connections, we controlled for co-occurring symptoms with a voxel-wise partial correlation between the functional maps of lesions of each symptom group and the remaining functional maps of lesions that caused psychosis. We used voxel-wise permutation-based correction for multiple comparisons using the Westfall-Young procedure ($p_{FWE} < 0.05$).

Distinctions between different symptoms of psychosis in isolation

To determine if isolated psychotic symptoms mapped to areas distinct from the same symptoms presenting as part of a syndrome, we examined each cohort of lesions that caused psychotic symptoms in isolation. We performed LNM on each of these cohorts, with thresholds of >85% overlap of functional connections for the sensitivity test and $p_{FWE}<0.05$ for the voxel-wise two-sample t-test against controls for the specificity test.

Distinguishing networks of lesions that cause amnesia and lesions that cause amnesia with psychosis

We first examined the 53 cases used to derive a memory circuit (*25*) to identify if any of them had psychotic symptoms. We also examined the 155 cases used for this psychosis circuit to identify how many had amnestic symptoms.

We then compared the functional connectivity of lesions that caused psychosis and amnesia with the functional connectivity of lesions that just caused amnesia using a two- sample t-test at each voxel. We used the FWE method ($p_{FWE} < 0.05$) to correct for multiple comparisons.

To determine if laterality of lesions to different cerebral hemispheres could play a role in distinguishing between lesions that cause psychosis and amnesia and lesions that cause just amnesia, we used the Brainnetome Atlas to determine the number of voxels each lesion had in each hemisphere. We then categorized lesions based on if they were located in the right hemisphere, the left hemisphere, or both, and performed a chi-squared test to determine significance.

Validation in independent cohort

We used the Vietnam Head Injury Study (*31*) for external validation. This dataset has lesions from 181 Veterans who completed the neurobehavioral rating scale subsequent to penetrating brain trauma during the Vietnam War. Of the categories in the behavioral rating, "suspiciousness", "unusual thought content", "hallucinatory behavior", and "conceptual disorganization" describe positive symptoms of psychosis. "Hallucinatory behavior" was excluded from our analysis because only 2 of 181 patients in the VHIS were rated as displaying hallucinatory behavior, and both were given a 1 ("very mild") out of 6 on a Likert scale.

“Conceptual disorganization” was included in the analysis but was less specific than “unusual thought content” as a psychotic symptom because all the participants who were rated as having “unusual thought content” (n=21) were also rated as having “conceptual disorganization”, but many patients rated as having “conceptual disorganization” were not rated with “unusual thought content” (n=44/61). The criteria for “conceptual disorganization” included symptoms not specific to psychosis such as tangential and perseverative speech. We therefore hypothesized that of “unusual thought content” and “suspiciousness” as psychosis-like symptoms, and treated the other categories as controls. We estimated the functional connectivity of each lesion using the same normative database of resting-state functional connectivity (n=1000) as in our previous analyses. We correlated the functional maps of these lesions with their associated behavioral ratings and the map produced from the LNM specificity analysis, yielding a correlation between the psychosis circuit and the behavioral rating associated with brain lesions in an independent dataset. We hypothesized that lesions with greater connectivity to the psychosis circuit would be associated with psychosis-like symptoms but not other symptoms.

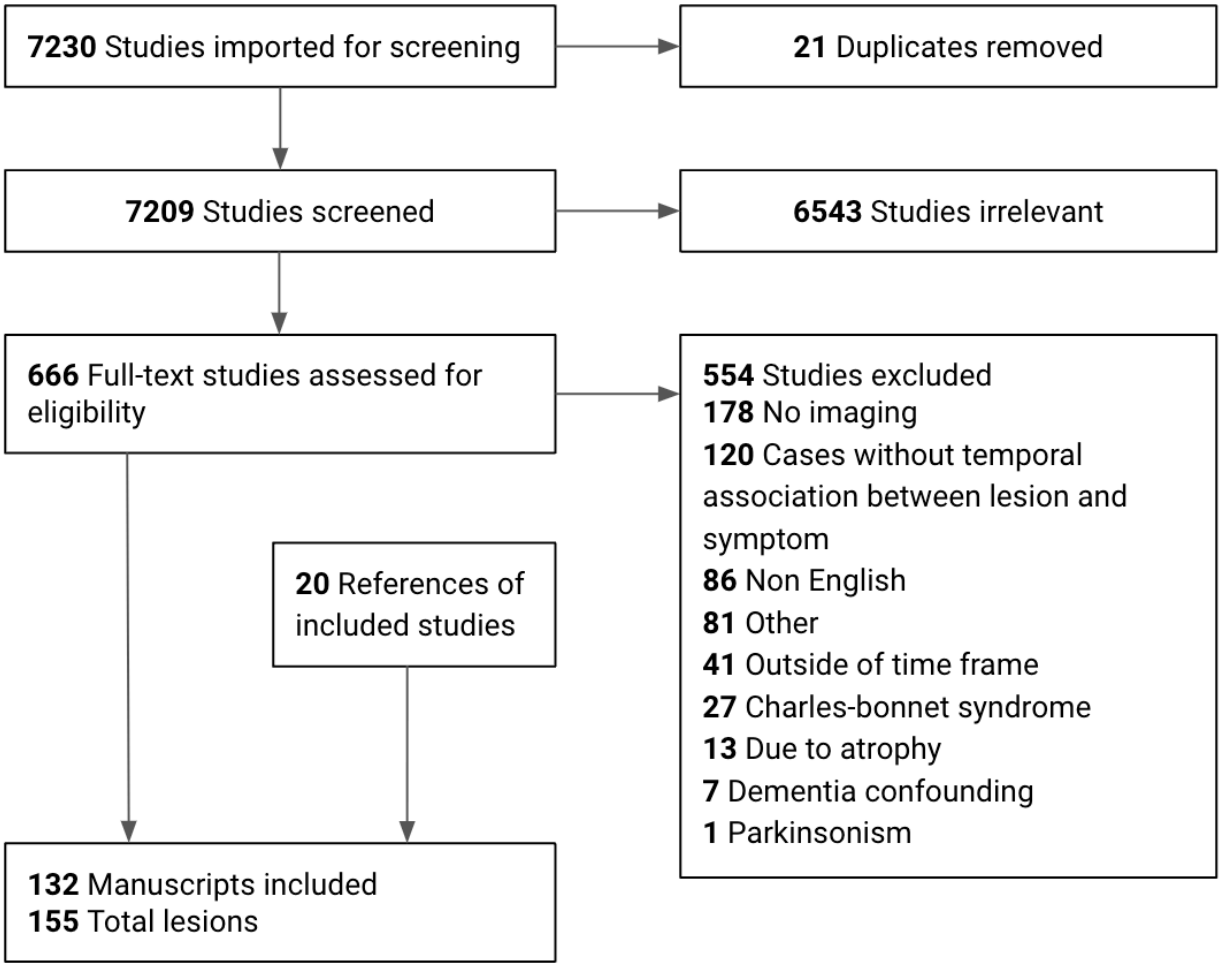
Lesion Network Mapping - determination of therapeutic target

To determine a therapeutic target, we constructed a precomputed functional connectome by computing average Blood Oxygenation Level Dependent (BOLD) signal correlations for each voxel across 1,000 participants. This generated a brain-wide functional map distinct for each voxel showing the BOLD correlations with the other 228,453 voxels in a 2mm-resolution brain atlas. We then correlated the functional map of each voxel with the functional map generated by the specificity test to look for the voxels whose BOLD correlations across the brain most closely resembled the functional map specific to lesions that cause psychosis. This method has

retrospectively replicated known therapeutic neuromodulation targets for depression (*20*) and addiction (*22*), but has not yet been used prospectively to identify novel therapeutic targets.

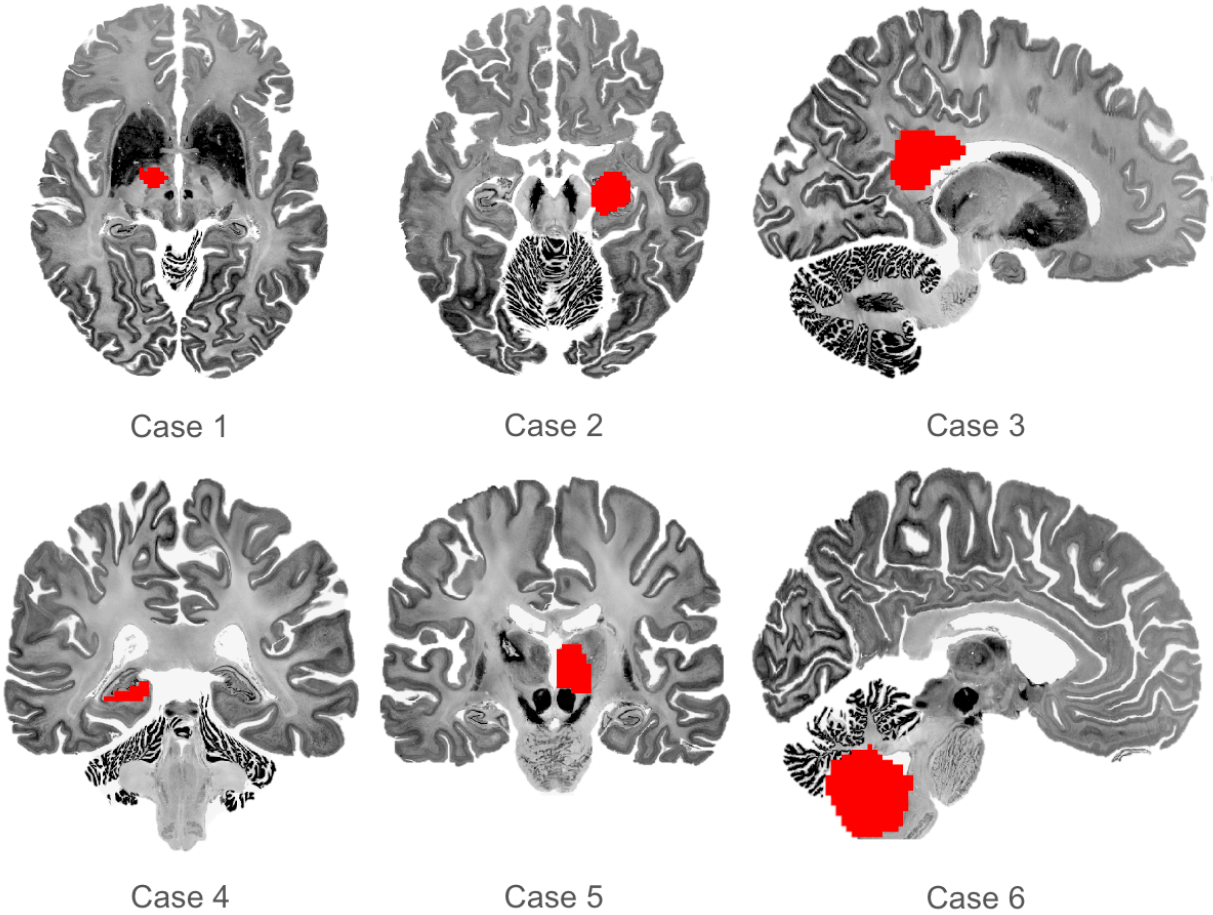
Supplementary Figures

Supplemental Figure 1
Results of PRISMA-formatted literature review

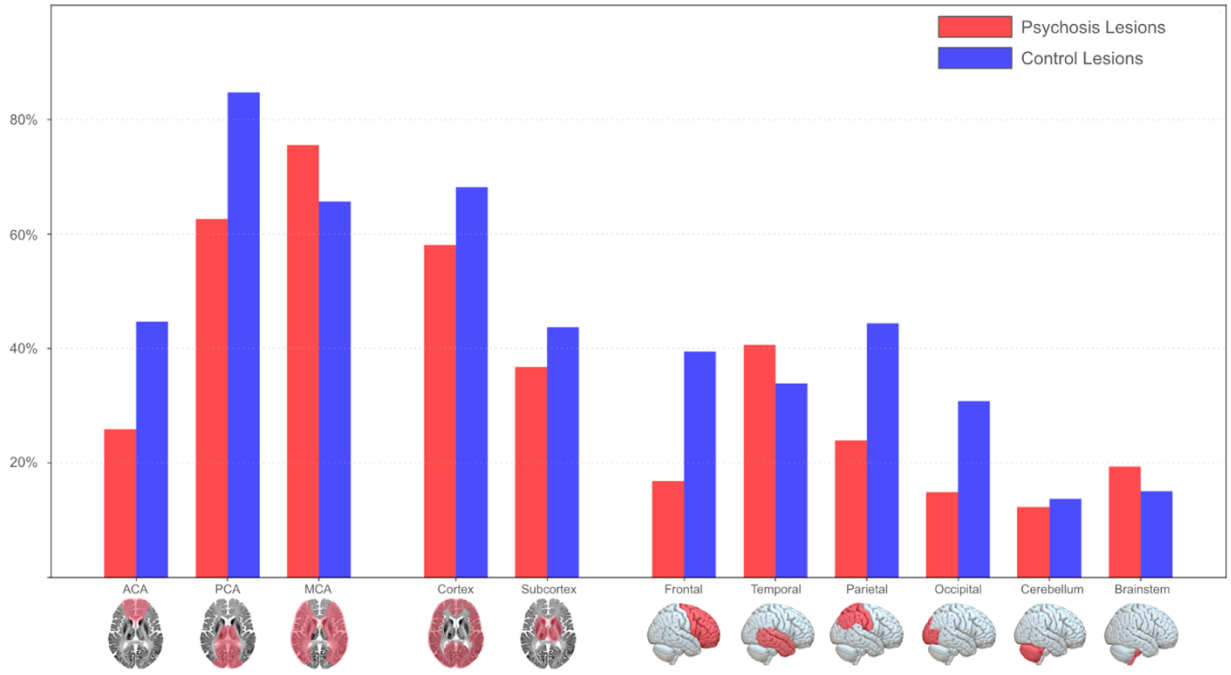


We identified lesions causing psychosis via a PubMed search including case reports, reviews, and systematic reviews published June, 1957- March, 2021 using the following search terms for All Fields:
(psychosis OR Schizophrenia OR hallucination OR hallucinosis) AND (lesion OR tumor OR tumour OR stroke OR infarct OR ischemic OR hemorrhage OR haemorrhage OR bleeding OR traumatic)

Supplemental Figure 2
Example Lesions Associated with Psychosis (6 of 155)

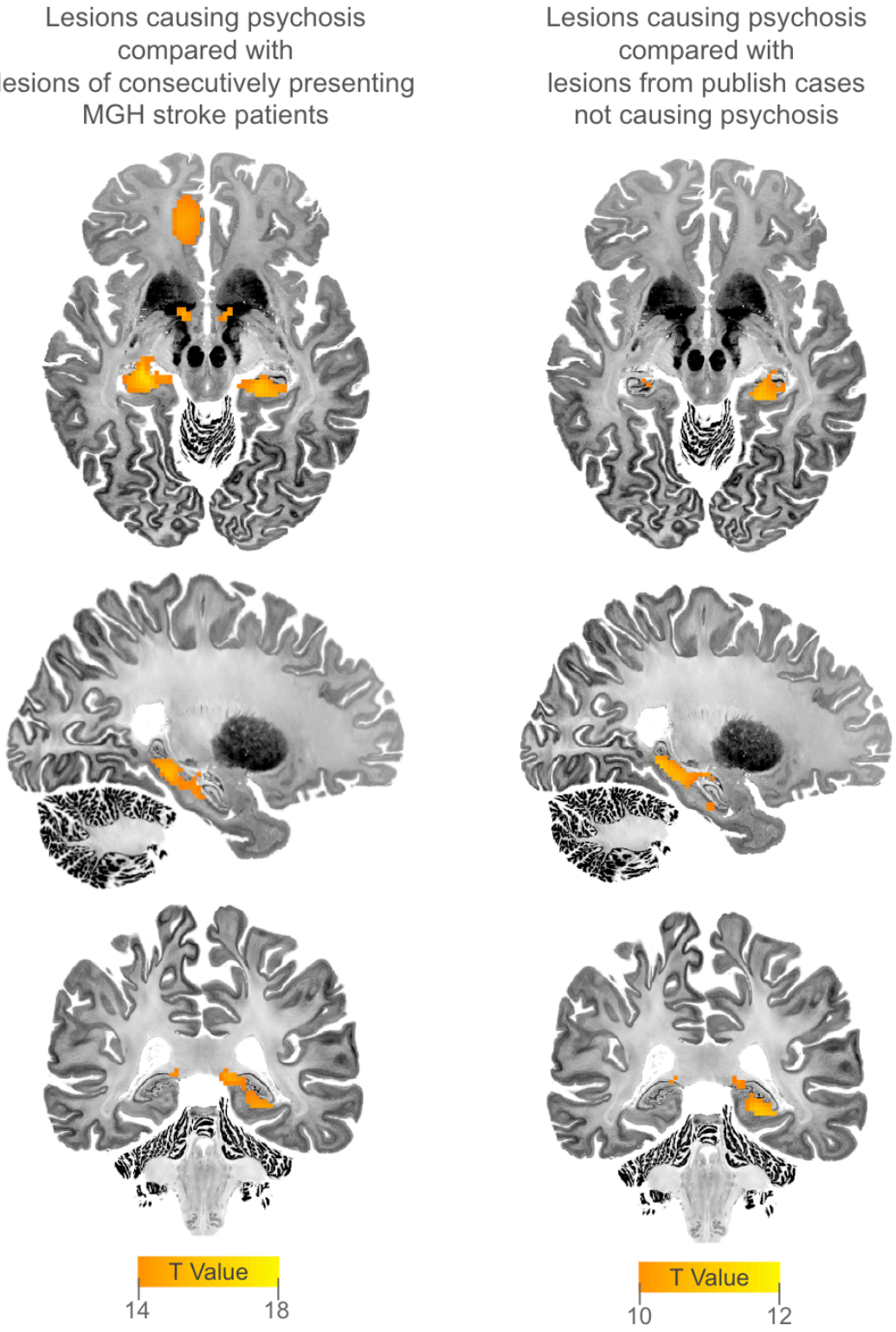


Supplemental Figure 3
Lesions associated with psychosis and control lesions were distributed throughout vascular territories and brain regions.

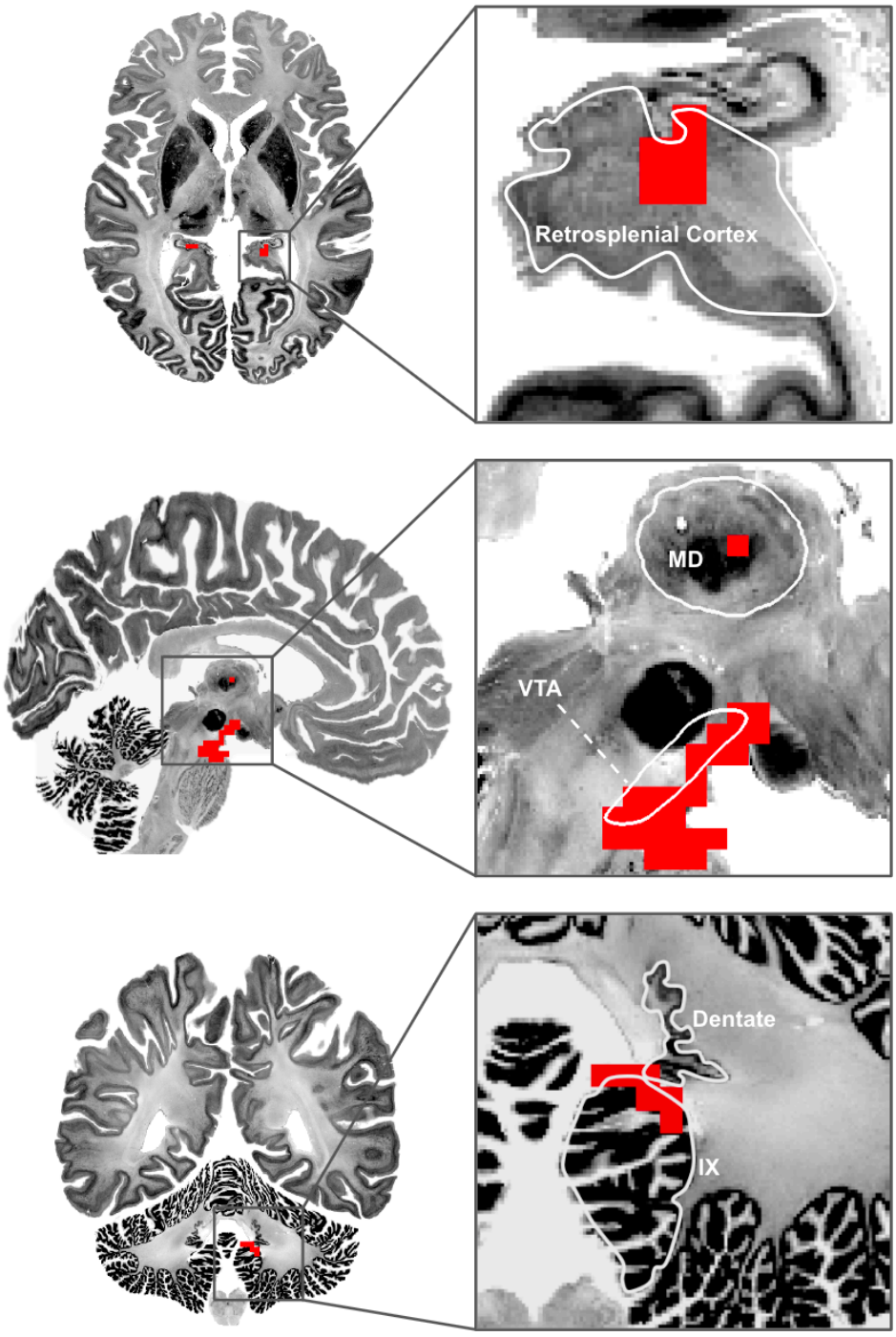


Distribution of lesions to cortex, subcortex, lobes, and vascular territories; illustrated as percentage of total lesions with voxels within each region. ACA=Anterior Cerebral Artery; PCA=Posterior Cerebral Artery; MCA=Middle Cerebral Artery.

Supplemental Figure 4
Voxel-wise two-sample t-test between lesions that cause psychosis and control lesions not associated with psychosis.



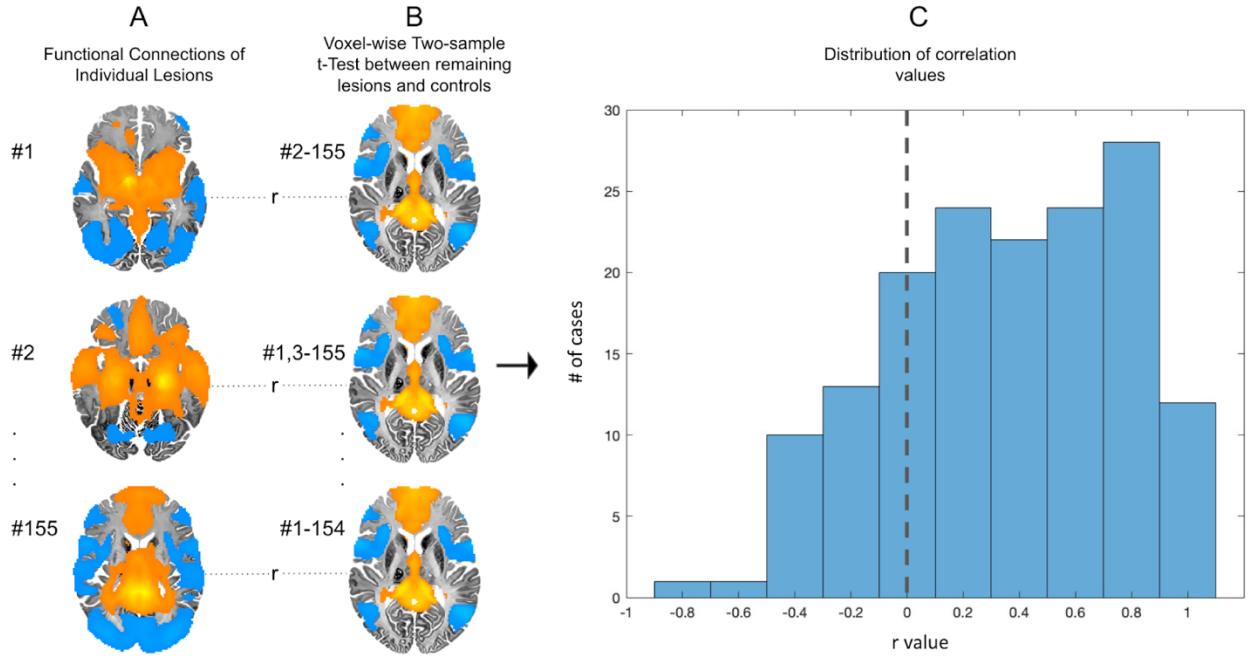
Supplemental Figure 5
Secondary Peak Regions of Psychosis Circuit



Convergence map depicting regions sensitive (overlap of functional connectivity of >70% of lesions) and specific (two-sample t-test ($p_{FWE}<1 \times 10^{-4}$) comparing functional connectivity of lesions that cause psychosis and control lesions) to a circuit affected by lesions that cause psychosis. MD=Mediodorsal Nucleus of the Thalamus; VTA=Ventral Tegmental Area. Dentate=Dentate Nucleus of the cerebellum; IX=Lobule IX of the cerebellum

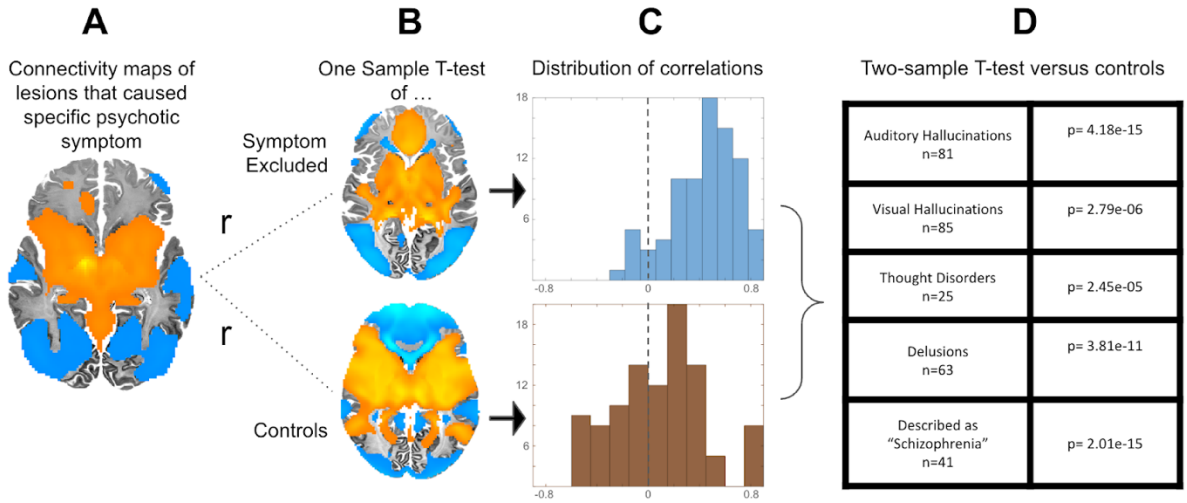
Supplemental Figure 6

Leave-one-out analysis, leaving out the functional map of each lesion



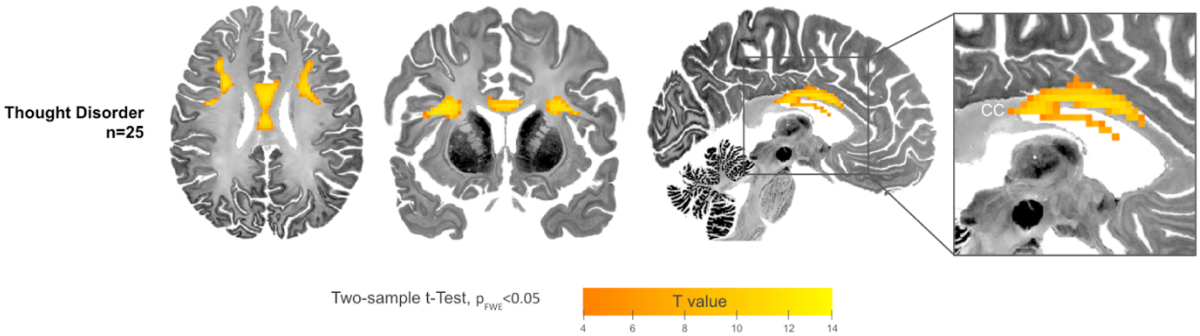
a)The functional connections of each lesion **b)** a voxel-wise two-sample t-test between the remaining 154 lesions and the control group **c)** a histogram displaying the distribution of spatial correlation values between the functional connections of each lesion and the specificity map generated from the functional connections of the remaining 154 lesions.

Supplemental Figure 7
Different symptoms of psychosis map to common circuitry



(a) Representative example of functional connectivity of a lesion causing a psychotic symptom **(b)** connectivity maps of each symptom group were correlated with a map of mean connectivity of lesions that cause psychosis without the symptom being tested and mean connectivity of control lesions. **(c)** Distribution of correlations of each lesion to each of the two comparator groups. Y axis=number of cases; X axis=r value (Range: -1 to 1. The zero value is marked with a dotted line) **(d)** For each psychotic symptom, lesion connectivity was more similar to other psychotic symptoms than to control symptoms.

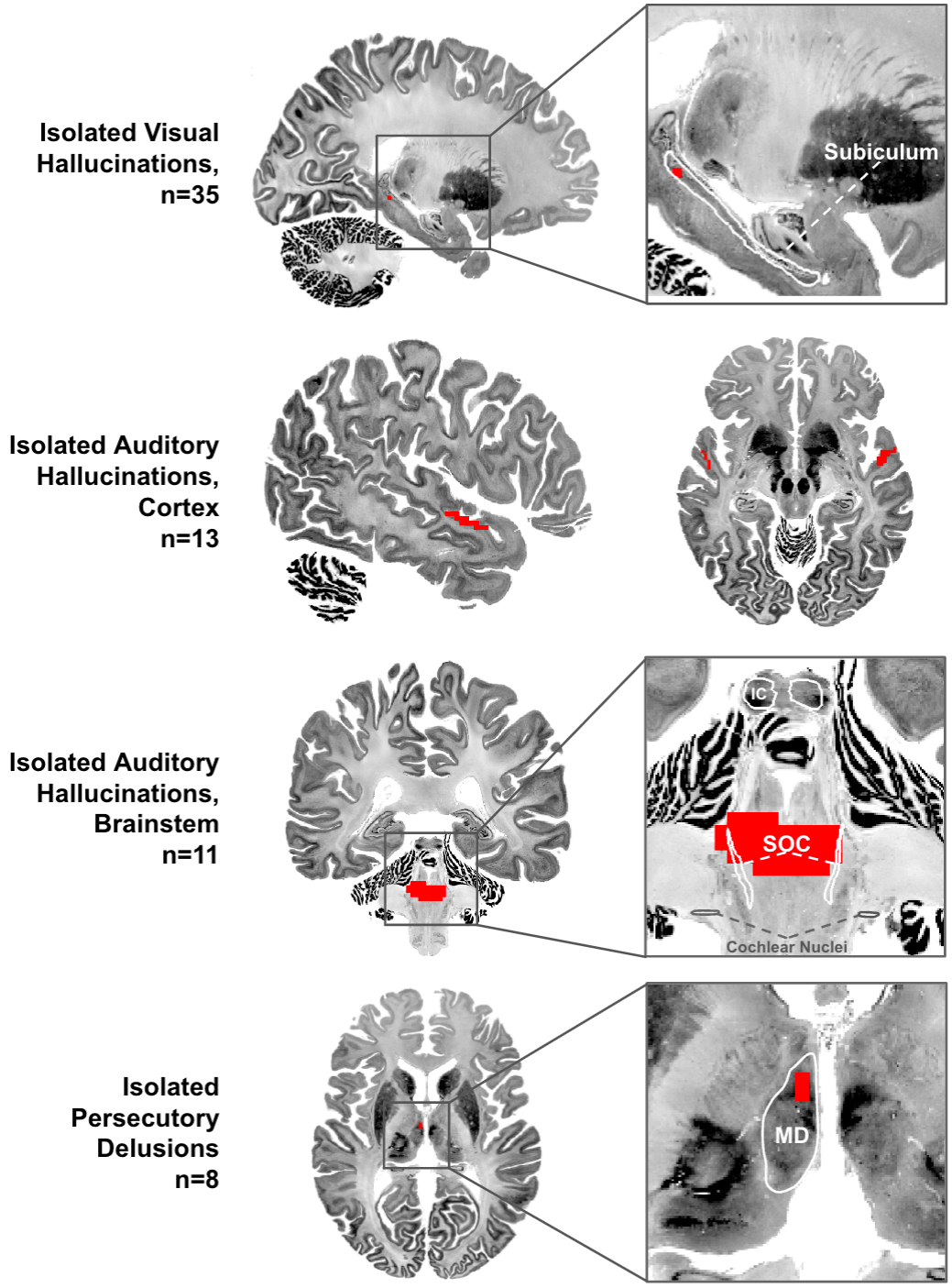
Supplemental Figure 8
Lesions that cause thought disorder map to different regions of a similar circuit.



Voxel-wise two-sample t-tests between functional networks of lesions that cause thought disorder and lesions that cause other symptoms of psychosis (p_{FWE}<0.05). CC= Corpus Callosum

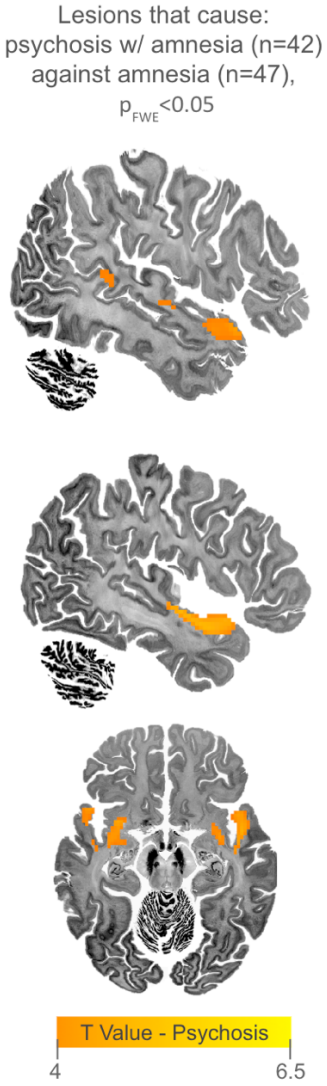
Supplemental Figure 9

Lesions that cause isolated symptoms of psychosis map to distinct regions.



Conjunction of functional network overlap (>85%) and voxel-wise two-sample t-tests between each symptom group and controls ($p_{FWE}<0.05$). Isolated visual hallucinations localize to the subiculum; isolated auditory hallucinations localize to the superior temporal gyrus or structures and lateral lemniscus white matter pathways of the subcortical auditory system (*89*); isolated delusions localize to the right mediodorsal nucleus of the thalamus. IC=Inferior Colliculus; SOC=Superior Olivary Complex; MD=Mediodorsal Nucleus of the Thalamus

Supplemental Figure 10
Voxel-wise two-sample t-tests comparing lesions that cause psychosis with amnesia and lesions that cause only amnesia.



Voxel-wise two-sample t-test (p_{FWE}<0.05) comparing connectivity maps of lesions that cause psychosis and amnesia and lesions that cause just amnesia. Lesions that cause psychosis and amnesia are more functionally connected to aspects of the superior temporal gyrus, the ventral claustrum, and part of the uncinate fasciculus, compared with lesions that cause just amnesia.

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