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A Neural Circuit for Spirituality and Religiosity Derived From Patients With Brain Lesions

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ABSTRACT

BACKGROUND: Over 80% of the global population consider themselves religious, with even more identifying as spiritual, but the neural substrates of spirituality and religiosity remain unresolved.

METHODS: In two independent brain lesion datasets (N_1 = 88; N_2 = 105), we applied lesion network mapping to test whether lesion locations associated with spiritual and religious belief map to a specific human brain circuit.

RESULTS: We found that brain lesions associated with self-reported spirituality map to a brain circuit centered on the periaqueductal gray. Intersection of lesion locations with this same circuit aligned with self-reported religiosity in an independent dataset and previous reports of lesions associated with hyper-religiosity. Lesion locations causing delusions and alien limb syndrome also intersected this circuit.

CONCLUSIONS: These findings suggest that spirituality and religiosity map to a common brain circuit centered on the periaqueductal gray, a brainstem region previously implicated in fear conditioning, pain modulation, and altruistic behavior.

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Spiritual and religious behaviors have been present since early stages of human evolution (1) and played a significant role in shaping most human societies (1–5). Today, over 80% of the global population identify as religious, and even more as spiritual (2,6). Defining and measuring these behaviors scientifically is possible. Spirituality, or more precisely, spiritual acceptance, has been defined as “a stable shift in worldview towards belief in forces that cannot be rationally comprehended or objectively proven.” (7,8) It has been measured using the Temperament and Character Inventory, which includes questions about “being directed by a spiritual force,” “miracles,” “religious experiences,” and “purpose.” Religiosity has been defined as participation in a “unified system of beliefs and practices relative to sacred things.” (3) There is no accepted standard for measuring religiosity, but it can be assessed via simple self-report to the question “Do you consider yourself to be a religious person?” (9).

The biological basis for spirituality and religiosity has been investigated using genetics, neurotransmitter levels, and functional neuroimaging (10–16). Functional neuroimaging has identified many different brain regions whose activity is correlated with spirituality or religiosity, but whether these regions are causally involved in these behaviors is unknown.

Patients with brain disorders can provide unique insight into the neural substrate of spirituality and religiosity that can complement data from functional neuroimaging (17–23). Patients with temporal lobe epilepsy can present with hyper-religious symptoms (18–21), which has been linked to hippocampal as opposed to amygdala pathology (24). Patients with parietal lobe damage can experience increased spirituality (22), and patients with frontal lobe damage can show increased religious fundamentalism (23,25). Such patients can allow for causal inferences between neuroanatomy and spiritual or religious behaviors, but multiple different brain regions have been implicated.

Recently, it has become possible to map complex behavior to human brain circuits based on locations of brain damage that modulate the behavior and a wiring diagram of the human brain termed the human connectome (26). This technique, termed lesion network mapping, is particularly helpful when lesions causing similar symptoms occur in multiple different brain locations. Lesion network mapping has identified human brain circuits associated with amnesia, delusions, hallucinations, and even disorders of free will (27–30). Here, we used this technique to test whether lesion locations associated with spiritual and religious belief map to a specific human brain circuit.

METHODS AND MATERIALS

Lesion Dataset for Spiritual Acceptance

We analyzed a previously published dataset (22) in which neurosurgical patients were recruited for the purpose of studying temperament and character changes after brain tumor resection (N = 88) (Figure 1) (Supplemental Methods). For the current study, we focused on the spiritual acceptance

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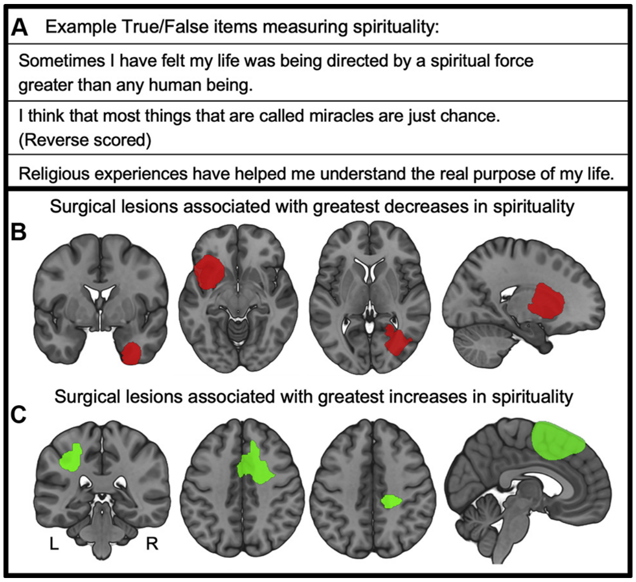

Figure 1. Lesion locations associated with changes in spirituality occur in many different brain locations. **(A)** Spirituality (or, more precisely spiritual acceptance) is measured by the Temperament and Character Inventory using a series of true or false self-report items. Spirituality is calculated as a single-value score based on participant responses across the items. Spirituality scores were obtained before and after neurosurgical resection of brain tumors, and changes in spirituality calculated from these longitudinal time points. **(B)** Lesion locations from the 4 patients with the greatest decrease in spiritual acceptance after neurosurgery. **(C)** Lesion locations from the 4 patients with the greatest increase in spiritual acceptance. L, left; R, right.

subscale of the self-transcendence domain because it has previously been validated as a metric of spirituality and religiosity (8,10,13). Note that this differs from a previous report on this dataset (22), which focused on the broader self-transcendence category.

Lesion Network Mapping of Spiritual Acceptance

We used lesion network mapping and previously validated methods to derive a brain network for spiritual acceptance in a data-driven fashion (26,27) (Figure 2). First, resting-state functional connectivity between each lesion location and the rest of the brain was computed using a publicly available normative connectome dataset from 1000 healthy right-handed subjects (42.7% male subjects, ages 18–35 years, mean age 21.3 years) (31,32). This connectome dataset was processed in accordance with the strategy of Fox *et al.* (33), which results in a map of brain regions functionally connected to each lesion location referred to as a lesion network (26,27). Second, we identified the peak connection most associated with changes in spiritual acceptance using voxelwise permutation analysis of linear models (PALM) with changes in spiritual acceptance as a behavioral covariable (Figure 2). The peak voxelwise association was identified and the coordinates recorded in Montreal Neurological Institute (MNI) space. By definition, functional connectivity with this peak coordinate (using the same normative connectome described above) defines a brain network that best aligns with lesion locations decreasing or increasing spirituality. We previously used this same approach to define brain networks for memory (27) and depression (34). Because we were searching for the peak voxelwise association to define a spirituality network, this analysis was not corrected for multiple comparisons across all brain voxels. This peak should therefore be considered descriptive until validated in an independent dataset.

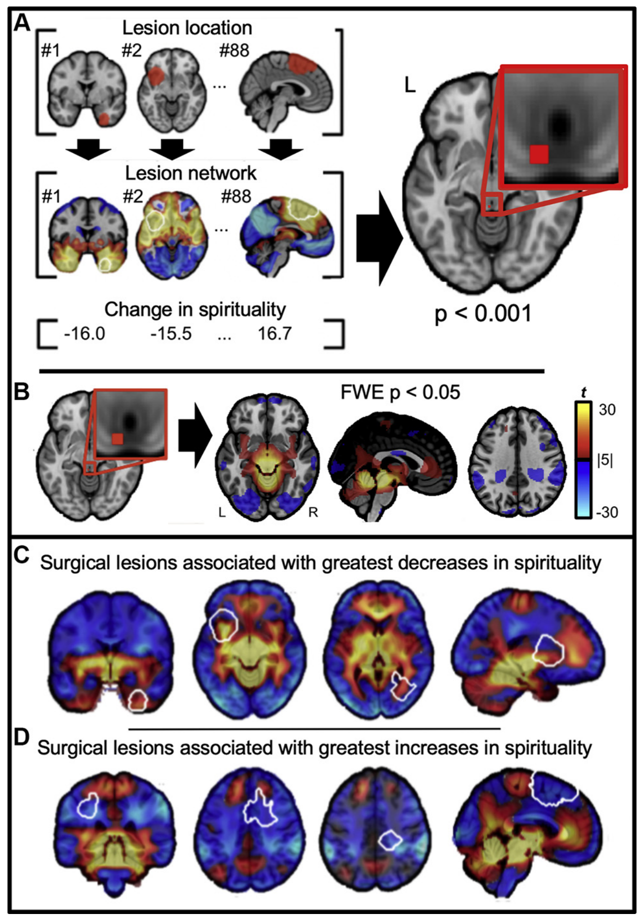

Figure 2. Data-driven method for identifying a lesion network for spiritual acceptance. **(A)** The network of brain regions functionally connected to each lesion location was computed using resting-state functional connectivity data from a large database of healthy volunteers (N = 1000). Lesion locations and lesion networks are shown for 3 of the 88 neurosurgical cases. Positively connected voxels are shown in warm colors, while negatively connected voxels are shown in cool colors. The peak voxelwise association between lesion connectivity and changes in spiritual acceptance was identified (image shown at uncorrected $p < .001$). **(B)** Functional connectivity with this peak was computed using the same resting-state functional connectivity database from healthy volunteers (N = 1000) to derive a brain circuit for spirituality (image shown after voxelwise correction for multiple comparisons, familywise error [FWE]-corrected $p < .05$). **(C, D)** Circular demonstration that our brain circuit for spirituality aligns with lesion locations associated with decreased spirituality **(C)** or increased spirituality **(D)**. Lesions locations associated with increased spirituality intersect negatively connected regions (cool colors), while legions associated with decreased spirituality intersect positively connected regions (warm colors).

To test for robustness, we repeated this PALM analysis including lesion size as a covariate. To test for specificity to spiritual acceptance, we repeated this PALM analysis using all seven Temperament and Character Inventory measures available in this dataset as covariates while also controlling for lesion size.

Validation in an Independent Dataset

To validate these data-driven findings, we analyzed a second independent dataset from patients with lesions caused by penetrating head trauma from combat during the Vietnam War (N = 105). Religiosity was assessed via questionnaire ("Do you consider yourself to be a religious person?"; yes or no) administered several decades after brain injury, during phase 4 of the Vietnam Head Injury Study (35). Lesion locations were outlined on computed tomography scans and transformed to MNI space as described previously (35).

We calculated functional connectivity between each head trauma lesion location (n = 105) with the peak coordinate identified from our neurosurgical dataset. In other words, the data-driven result from our neurosurgical dataset (discovery) was used as an a priori region of interest in the analysis of our independent head trauma dataset (validation). Using our normative connectome and previously reported methods (36), we computed the Pearson correlation between functional magnetic resonance imaging time-series extracted from each lesion location with the time-series extracted from our a priori region of interest. The resulting r values were converted to a normal distribution using Fischer's r-to-z transform, then averaged across the 1000 subjects, resulting in a single value that reflects the functional connectivity between each lesion location and our a priori region of interest (spirituality peak). We then used a two-sample two-tailed t test to compare connectivity values between nonreligiously self-identified individuals (n = 25) versus religiously self-identified individuals (n = 80).

In a related analysis, we tested whether intersection of lesion locations from our head trauma dataset (N = 105) with the spirituality circuit derived from our neurosurgical dataset was associated with religiosity. A circuit damage score was computed by overlapping each head trauma lesion (N = 105) with the circuit map defined by functional connectivity to the peak coordinate from the neurosurgical dataset (N = 88). We then calculated the sum of functional connectivity values for all voxels within the lesion trace (34,37). We again used a two-sample two-tailed t test to compare circuit damage score values between nonreligiously self-identified (n = 25) versus religiously self-identified (n = 80) individuals. For visualization purposes, we overlaid lesion locations from nonreligious versus religious individuals on the brain circuit derived from our spirituality dataset (Figure 3).

Swapping Discovery and Validation Datasets

To ensure that results were not dependent on which dataset we used for discovery versus validation, we repeated analyses using the head trauma dataset to define a data-driven network for religiosity (discovery) and the independent neurosurgical dataset to test whether this network was related to lesion-induced changes in spirituality (validation). For a more detailed description, see Supplemental Methods.

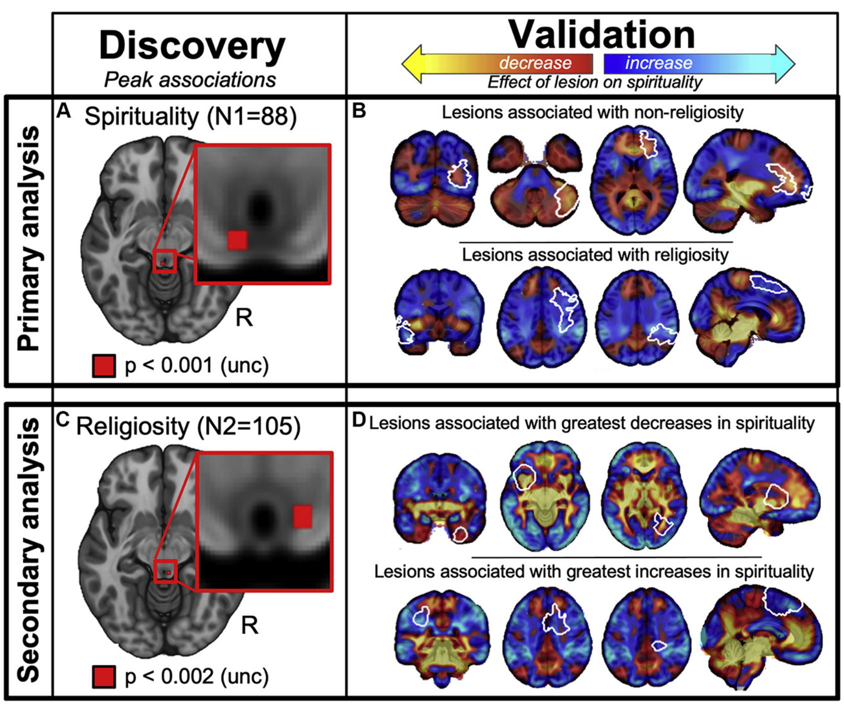

Figure 3. Cross-validation of lesion network mapping results across two independent datasets. **(A)** Discovery: lesion network mapping of spiritual acceptance in a neurosurgical dataset (N = 88) identified a peak association in the periaqueductal gray (PAG) (uncorrected [unc] $p < .001$; $z = -10$). **(B)** Cross-validation: functional connectivity between this PAG location and lesion locations from an independent dataset of head trauma lesions (N = 105) was associated with religiosity (white outlines showing 8 of 105 lesions). Positive functional connectivity with the PAG is shown in warm colors (intersecting lesion locations associated with nonreligiosity), while negative functional connectivity with the PAG is shown in cool colors (intersecting lesion locations associated with religiosity). **(C)** Discovery: lesion network mapping of religiosity in a head trauma dataset (N = 105) also identified a peak association in the PAG (unc $p < .002$; $z = -11$). **(D)** Cross-validation: functional connectivity between this PAG location and lesion locations from an independent dataset of neurosurgical lesions (N = 88) was associated with changes in spirituality (white outlines showing 8 of 105 lesions). Positive functional connectivity with the PAG is shown in warm colors (intersecting lesion locations associated with decreased spirituality), while negative functional connectivity with the PAG is shown in cool colors (intersecting lesion locations associated with increased spirituality). R, right.

Voxel-Based Lesion Symptom Mapping

To test whether or results depended on connectivity or could be obtained based on lesion location alone, we repeated all analyses using voxel-based lesion symptom mapping (VLSM) (see Supplemental Methods).

Robustness to Methodological Changes

To ensure that our lesion network mapping results were not dependent on methods used for processing resting-state functional connectivity, we repeated our analyses using a human connectome processed without global signal regression (Supplemental Methods) (36). We repeated lesion network mapping analysis for spirituality (in the neurosurgical dataset) and religiosity (in the head trauma dataset) using this alternative connectome.

To ensure that our lesion network mapping results were not dependent on the peak voxel, we repeated our lesion network analyses using the top 1% and 5% of voxels rather than only the peak voxel. This analysis was performed separately on our spirituality dataset and our religiosity dataset, each processed using two different connectome processing strategies described above. This resulted in 8 total maps (4 maps with the 1% cutoff and 4 maps at the 5% cutoff). Of these four maps for each voxel cutoff, two maps were voxelwise associations with spirituality (with and without global signal regression) and two maps were voxelwise associations with religiosity (with and without global signal regression). We performed a conjunction analysis by binarizing each map and overlapping them, showing results that are independent of dataset and these methodological changes (Figure 4).

Characterization of the Spirituality Network

We identified local maxima in our spirituality network using a clustering analysis (FSL, version 6.0, 2018 release). No a priori threshold was applied for clustering or local maxima searching. The top ten positive and negative peaks were identified and recorded.

Literature-Based Case Reports of Hyper-religiosity

Case reports of patients with lesion-induced hyper-religiosity were identified using a systematic literature search (see Supplemental Materials). Lesion location was traced by hand from the published image onto the MNI template brain using 3D Slicer (available at https://www.slicer.org) (Figure 5). Although previous work has shown high test-retest reproducibility of these tracings (37), the tracings were repeated by a second person blinded to the lesion network mapping results of this study (Figure S3). Intersections of each lesion location with our spirituality circuit were quantified by summing the t values of each voxel in our spirituality circuit that fell within each lesion trace (34).

Relationship to Hyper-religiosity in Temporal Lobe Epilepsy

To explore whether spirituality circuit topography aligns with previously published descriptions of hyper-religiosity in the context of mesial temporal lobe epilepsy (24), we leveraged a previous study linking hyper-religiosity to neuroanatomy (24). Specifically, hyper-religiosity was associated with hippocampal but not amygdala atrophy. We therefore computed the intersection of our circuit with anatomical masks of the hippocampus and the amygdala from the Harvard-Oxford neuroanatomical atlas. Intersection was quantified by summing the t values of each voxel in our spirituality circuit that fell within the hippocampus and amygdala masks (34).

Relationship to Lesions Associated With Other Neurologic or Psychiatric Symptoms

Spirituality circuit damage scores were calculated as described above for 356 symptom-causing lesions spanning 12 unique symptoms (Figure 6) (34,37). These 12 symptoms represent all lesion network mapping studies previously published by our laboratory at the time of this manuscript preparation. In other words, these symptoms were not selected on the basis of any a priori hypothesis for which symptoms should align with our spirituality and religiosity circuit. These 12 queried symptoms included akinetic mutism (n = 28) (30), alien limb (n = 50) (30), amnesia (n = 53) (27), asterixis (n = 30) (38), criminality (n = 17) (19), delusions (n = 15) (39), expressive aphasia (n = 12) (29), freezing of gait (n = 14) (40), hallucinations (n = 15) (41), hemichorea (n = 29) (40), pain (n = 24) (29), and parkinsonism (n = 29) (42). A one-way analysis of variance was performed across symptom categories to test for preferential relationships between specific categories of symptom-causing lesions and the spirituality circuit. Post hoc one-sample t tests were performed on spirituality circuit damage for each

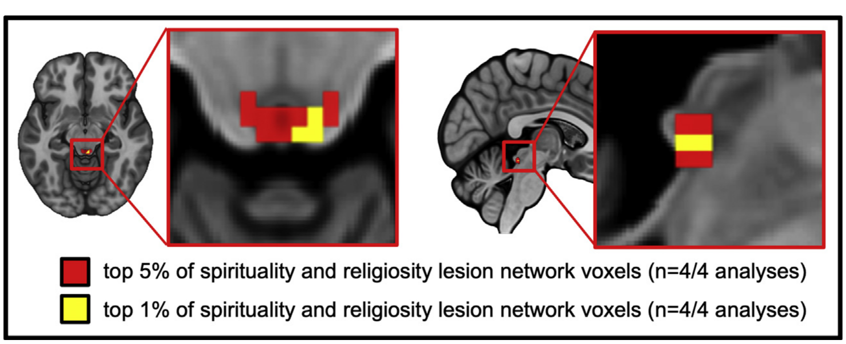

Figure 4. Conjunction of lesion network mapping results using different analysis approaches shows consistent localization to the periaqueductal gray: the top 5% of voxels (red) and top 1% of voxels (yellow) identified across our two independent datasets analyzed using two different connectome processing strategies (i.e., connectomes processed either with or without global signal regression).

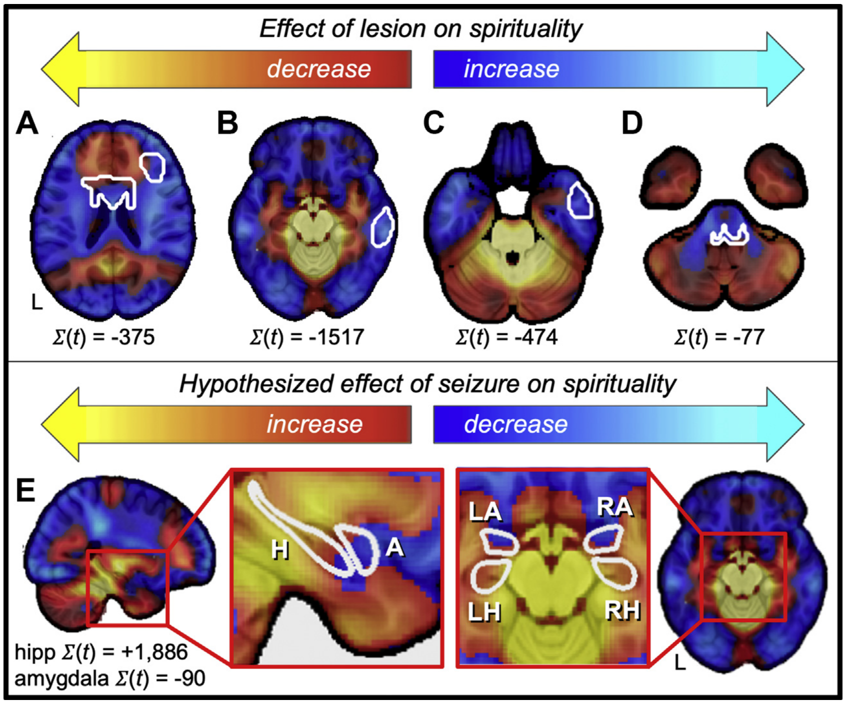

Figure 5. Our brain circuit for spiritual acceptance aligns with previous literature on hyper-religiosity. **(A–D)** Case reports of lesion locations associated with hyper-religiosity (white outlines) intersect negative nodes of our spirituality circuit. **(E)** Brain regions previously associated with seizure-induced hyper-religiosity (hippocampus [H]) intersects positive nodes of our spirituality circuit, but not adjacent brain regions not associated with hyper-religiosity (amygdala [A]). Positive periaqueductal gray connectivity is shown in warm colors, while negative periaqueductal gray connectivity is shown in cool colors. L, left; R, right.

individual symptom to quantitatively characterize the relationships between symptom-causing lesions and the spirituality circuit.

RESULTS

Lesion Network Mapping of Spiritual Acceptance

Of the 88 neurosurgical patients, 30 patients showed a decrease, 29 showed an increase, and 29 showed no change in self-reported spiritual belief before and after neurosurgical brain tumor resection (Tables S1 and S2) (7,22). Lesion locations were heterogeneously distributed throughout the brain (Figure 1B, C).

Using lesion network mapping (Figure 2), the peak association with changes in spiritual acceptance was connectivity between lesion locations and the periaqueductal gray (PAG) (MNI: $x = -2$, $y = -36$, $z = -10$, uncorrected $p < .001$) (Figure 2A). Functional connectivity with this PAG location thus defines a brain circuit that best aligns with lesion locations that

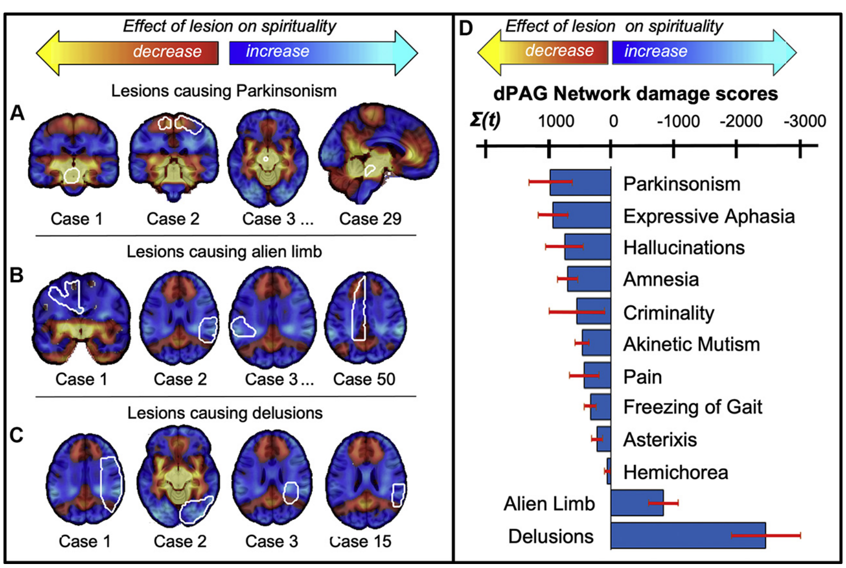

Figure 6. Lesion locations associated with other neurologic and psychiatric symptoms intersect our spirituality circuit. Lesion locations (white outlines) associated with parkinsonism (showing 4 of 29 cases) **(A)** intersected positive nodes of our spirituality circuit, similar to lesions associated with nonreligiosity. Lesion locations associated with alien limb syndrome (showing 4 of 50 cases) **(B)** and delusions (showing 4 of 15 cases) **(C)** showed the strongest intersection with negative nodes of our spirituality circuit, similar to lesion locations associated with religiosity. The sum of voxel intensities within lesion locations associated with 12 different neurologic and psychiatric symptoms (n = 356) are shown in a bar graph **(D)**. Error bars reflect standard error across different lesion locations within each lesion syndrome. dPAG, dorsal periaqueductal gray.

modulate spirituality (Figure 2B), such that lesion locations associated with decreased spirituality intersect positive nodes in this map, while lesion locations associated with increased spirituality intersect negative nodes (Figure 2C, D).

Connectivity between lesion locations and the PAG was still associated with changes in spirituality after controlling for lesion size (p = .002). Lesion connectivity to PAG was also specific for spiritual acceptance when controlling for all seven Temperament and Character Inventory measures of temperament and character (p = .02).

Validation in an Independent Dataset

Of the 105 patients who completed a questionnaire about religiosity after penetrating head trauma (Tables S1 and S2), 24% identified as nonreligious and 76% self-identified as religious. Functional connectivity between lesion locations in this independent dataset (N = 105) and the PAG hub of our spirituality circuit (defined using our neurosurgical dataset) was significantly associated with whether subjects self-identified as nonreligious or religious ($p < .01$). Circuit damage scores for damage caused by lesions in this independent dataset (N = 105) to the spirituality circuit (defined using our neurosurgical dataset) were also significantly associated with self-identification as nonreligious or religious ($p < .03$). To illustrate this cross-dataset convergence, we show lesion locations from the head trauma dataset overlaid on the spirituality circuit derived from our neurosurgical dataset (Figure 3B).

Swapping Discovery and Validation Datasets

Using our head trauma lesion dataset (N = 105) to derive a data-driven lesion network for religiosity, we again found a peak association in the PAG (MNI: x = 3, y = −35, z = −11, uncorrected $p < .002$) (Figure 3B). The peak association for religiosity in this independent dataset was within 4 mm of the peak association for spirituality (Figure 3A, C). As before, this relationship persisted after controlling for lesion size (p = .003) and was specific to religiosity when controlling for other behavioral measures (p = .003). Functional connectivity between neurosurgical lesion locations (N = 88) and the PAG hub of our religiosity circuit (defined in the independent head trauma dataset) was significantly associated with changes in spiritual acceptance ($p < .02$). Circuit damage scores for neurosurgical lesion damage to the religiosity circuit was also significantly associated with changes in spiritual acceptance ($p < .05$) (Figure 3D).

Voxel-Based Lesion Symptom Mapping

Using VLSM, no voxels were associated with changes in spiritual acceptance at the uncorrected threshold of $p < .001$ (matching the peak voxelwise association discovered from lesion network mapping) and no voxels were associated with self-identified religiosity at the uncorrected threshold of $p < .002$ (matching the peak voxelwise association discovered from lesion network mapping). Using the unthresholded VLSM maps and testing for cross-dataset validation, there was no association between our VLSM map for spirituality and lesion locations associated with religiosity (p = .98) and no association between our VLSM map for religiosity and lesion locations associated with changes in spiritual acceptance (p = .76).

Robustness to Methodological Changes

To ensure that our data-driven localization to the PAG was independent of our specific methods, we repeated our lesion network mapping analysis using a connectome processed without global signal regression, in each case looking at the top 1% and 5% of voxels rather than just the peak association. Results were robust to these processing changes, again identifying a brain circuit for spirituality and religiosity centered on the PAG (Figure 4).

Characterization of PAG Functional Connectivity Network

Our spirituality circuit (defined by functional connectivity to the PAG) includes positive connectivity to subcortical and limbic regions and negative connectivity to frontoparietal networks and cortical regions previously implicated in reasoning (for peak coordinates, see Table S3; for overlap images, see Figure S1).

Alignment With Previous Literature on Hyper-religiosity

Our systematic literature search identified four case reports of lesions associated with hyper-religiosity (Figure S2 and Table S4). Each lesion location intersected negative nodes of our brain circuit, similar to lesions from our initial datasets associated with increased spirituality or religiosity (Figure 5A–D). Exploratory analyses of brain regions linked to seizure-induced hyper-religiosity also align well with our circuit (Figure 5E).

Relationship to Lesions Associated With Other Neurologic or Psychiatric Symptoms

Finally, in our examination of 356 lesion locations associated with a range of other neurologic and psychiatric symptoms, we found that lesion locations associated with certain symptoms intersected our spirituality circuit more so than others (one-way analysis of variance, $F_{11} = 6.1$, $p = 10^{-8}$) (Figure 6). Specifically, lesions causing parkinsonism (t_{28} = 2.7, p = .01, 95% confidence interval [CI], 243 to 1668) intersected positive areas of our circuit, similar to lesions associated with decreased spirituality (Figure 6). Lesions causing delusions (t_{14} = −4.4, p = .001, 95% CI, −3667 to −1253) and alien limb syndrome (t_{49} = −3.5, p = .001, 95% CI, −1320 to −352) intersected negative regions on our map, similar to lesion locations associated with increased spirituality and religiosity (Figure 6).

DISCUSSION

Brain lesions associated with changes in spiritual acceptance map to a functionally connected brain circuit centered on the PAG. Intersection of lesion locations with this spirituality circuit was associated with self-reported religiosity in an independent dataset, intersected previous case reports of hyper-religiosity, and intersected lesion locations associated with delusions and alien limb syndrome.

Our finding that spirituality and religiosity map better to a functionally connected brain circuit than an individual brain region is consistent with recent results across a range of complex human behaviors (27–30) and may help explain why previous studies have implicated multiple different brain regions (6,14,15,17,43). Our spirituality circuit is defined by connectivity to one focal brain region (the PAG), similar to previous work identifying a memory circuit defined by connectivity to the subiculum or a depression circuit defined by connectivity to the left dorsal lateral prefrontal cortex (27,34). In each case, lesion locations disrupting the behavior map to a brain circuit, but the circuit is defined by connectivity to one specific brain region that may play a critical role in mediating the behavior.

The PAG has been implicated in numerous functions including fear conditioning (44), pain modulation (45), altruistic behaviors (46), and unconditional love (47). It is anatomically connected to both the limbic system and prefrontal cortex (46) and enriched in receptors implicated in pain regulation (e.g., mu-opioid) and pair bonding (e.g., oxytocin) (46,48,49). Although speculative, these classic PAG functions may align with aspects of spirituality and religiosity. For example, religiosity increases under threat or after natural disasters (50), consistent with the role of the PAG in fear conditioning (44). Spirituality can alleviate pain and augment placebo (51), consistent with the role of the PAG in opiate and nonopiate analgesia (45,52). Finally, spirituality and religiosity have been linked to, if not equated with, unconditional love (53,54), consistent with the role of the PAG in maternal and pair bonding (47,55–60), unconditional love (47), maternal love (61), nonsexual love (59), compassion (62), and the duration of long-term relationships (55). These findings of shared brain circuitry for spiritual acceptance and altruism are also convergent with the hypothesis that spiritual beliefs facilitated the expansion of prosociality over the course of human evolution (63). Therefore, although the PAG was not an a priori region of interest before our study, it has been implicated in many functions that could be relevant for spirituality and religiosity.

Notably, the negative functional topography in our PAG-defined circuit for spirituality and religiosity aligns with the frontoparietal control network (31), previously implicated in executive control, as well as brain regions previously implicated in neuroimaging studies of reasoning (Figure S1). This result is consistent with previous work suggesting that spiritual acceptance is the opposite of rational materialism (7,8) and previous work suggesting that negatively correlated brain networks represent opposing functions (33).

Medically, hyper-religiosity has been noted after focal brain lesions and in patients with mesial temporal lobe epilepsy for many decades (18–21). Lesion locations in these case reports align well with our spirituality circuit. It remains unclear whether seizure onset zones associated with hyper-religiosity align with our circuit and whether hyper-religiosity is driven by regional hyperactivity during seizures or hypoactivity between seizures (21). Our exploratory results support the former, as atrophy locations associated with hyper-religiosity intersect positive nodes of our spirituality circuit, while lesions associated with hyper-religiosity intersect negative nodes (24) (Figure 5). The fact that hyper-religiosity can resolve after resection of the medial temporal lobe further supports this finding (21). Whether seizure propagation to the PAG is related to hyper-religiosity is a testable hypothesis for future work but is potentially consistent with brainstem propagation of mesial temporal seizures (64,65) and atrophy of the PAG in patients with mesial temporal lobe epilepsy (66).

We also examined our database of lesions associated with neurologic and psychiatric symptoms to see which, if any, of these symptoms share neuroanatomy with spirituality. Similarities between lesions associated with delusions and increased spirituality suggest a shared neural substrate, potentially consistent with shared features such as strongly held fixed beliefs or the occurrence of religious content in patients with delusions (38,39,67,68). Our data also suggest a shared neural substrate between spirituality and alien limb phenomenon, both of which can be associated with feelings of control by an external agent (30,69). This relationship may have clinical value, such as surrendering to a higher power in the context of addiction treatment (70,71). Finally, our results suggest an inverse association between spirituality and lesions associated with parkinsonism, potentially consistent with decreased religiosity in patients with Parkinson's disease (72,73).

It is important to note that a shared neural substrate between two phenomena may be helpful for understanding shared features and associations, but these results should not be overinterpreted. For example, our results do not imply that religion is a delusion, that historical religious figures suffered from alien limb syndrome, or that Parkinson's disease arises due to a lack of religious faith. Similarly, our results have no bearing on the truth of any particular religious or spiritual belief.

There are several limitations in the current study. First, participants in both our spirituality and religiosity datasets came from predominantly Christian cultures, which may limit generalizability to other cultures and religious traditions, and our assessment of religiosity in our head trauma dataset was limited to a single yes/no question, which does not capture the wide variety of religious beliefs, behaviors, or contributing factors such as exposure to religiosity during their youth. Second, our religiosity dataset was mostly Caucasian, older males, which may not generalize to other races, ages, or genders. Third, we investigated spirituality and religiosity as single behaviors, but different aspects of spirituality and religiosity may map to different brain circuits, an important topic for future work (17,43). Fourth, our localization of spirituality and religiosity to a brain circuit centered on the PAG was a post hoc discovery in the neurosurgical dataset ($N = 88$), which did not survive correction for multiple comparisons across all brain voxels; however, this limitation is largely mitigated by validation and replication of this finding in a second independent dataset (head trauma dataset, $N = 105$), in which the PAG circuit from the neurosurgical dataset was used as an a priori hypothesis. Relatedly, the lesions that we studied do not directly intersect with the PAG, and PAG involvement is inferred from connectivity to lesion rather than from direct lesion location. Additionally, our lesion networks explain only a small amount of behavioral variance, and there are undoubtedly many other factors contributing to these complex behaviors. Finally, the function of the PAG is based largely on animal studies, and any relationship between these functions and features of religiosity and spirituality should be considered speculative.

Our data provide several testable hypotheses for future work. First, we hypothesize that intersection of neurosurgical lesions with our PAG circuit will explain variance in spirituality or religiosity measured before and after intervention (as in the neurosurgical dataset). Second, we hypothesize that intersection of stroke lesions with our PAG circuit will be associated with measures of spirituality and religiosity assessed after the lesion (as in the head trauma dataset). Finally, we hypothesize that intersection of seizure onset zones with our PAG circuit will be associated with the presence or absence of seizure-induced hyper-religiosity.

In conclusion, our study demonstrates that lesions associated with spirituality and religiosity map to a human brain circuit defined by connectivity to the PAG. This brain circuit aligns with lesion locations from previous case reports of hyper-religiosity and with lesion locations previously associated with strongly held fixed beliefs and feelings of control by an external agent.

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MAF and MDF conceptualized and designed the work. MAF, AC, SS, and MDF designed and developed methods. MAF, AC, and SS contributed to programming, software development, and implementation of computer code. MAF performed validation and formal analysis. JG, CU, and FF conducted data collection. MAF, FLWVJS, and SMM contributed to data curation. MAF prepared the original draft. MAF, FLWVJS, AC, SS, SMM, JAN, JG, CU, FF, and MDF reviewed and edited. MAF visualized data and prepared data presentation. MDF supervised research planning and execution. MAF and MDF coordinated project administration. AC and MDF acquired financial support for the project leading to this publication.

Data, code, and materials used in the analysis are available upon reasonable request.

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ARTICLE INFORMATION

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