Title: Lesion Network Localization of Free Will

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Abstract:

Our perception of free will is composed of a desire to act (volition) and a sense of responsibility for our actions (agency). Brain damage can disrupt these processes, but which regions are most important for free will perception remains unclear. Here, we study focal brain lesions that disrupt volition, causing akinetic mutism (N = 28), or disrupt agency, causing alien limb syndrome (N = 50), to better localize these processes in the human brain. Lesion locations causing either syndrome were highly heterogeneous, occurring in a variety of different brain locations. We next used a recently validated technique termed lesion network mapping to determine whether these heterogeneous lesion locations localized to specific brain networks. Lesion locations causing akinetic mutism all fell within one network, defined by connectivity to the anterior cingulate cortex. Lesion locations causing alien limb fell within a separate network, defined by connectivity to the precuneus. Both findings were specific for these syndromes compared to brain lesions causing similar physical impairments but without disordered free will. Finally, our lesion-based localization matched network localization for brain stimulation locations that disrupt free will, and neuroimaging abnormalities in patients with psychiatric disorders of free will without overt brain lesions. Collectively, our results demonstrate that lesions in different locations causing disordered volition and agency localize to unique brain networks, lending insight into the neuroanatomical substrate of free will perception.

Significance Statement:

Free will consists of a desire to act (volition) and a sense of responsibility for that action (agency), but the brain regions responsible for these processes remain unknown. We found that brain lesions that disrupt volition occur in many different locations, but fall within a single brain network, defined by connectivity to the anterior cingulate. Lesions that disrupt agency also occur in many different locations, but fall within a separate network, defined by connectivity to the precuneus. Together, these networks may underlie our perception of free will, with implications for neuropsychiatric diseases in which these processes are impaired.

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Long the domain of philosophy, free will can be investigated scientifically (1–6). Experiments such as those by Benjamin Libet sparked debate regarding whether free will exists or is an illusion (1–3). This debate remains unsettled, but most agree that we perceive our actions to be freely willed (4–6). Recent investigations have therefore focused on understanding this perception, dividing it into two processes: the intention or motivation to act, referred to as volition (5); and the sense of responsibility for one's action, referred to as agency (4).

Many approaches have been used to identify brain regions involved in the perception of volition or agency. For example, direct electrical stimulation to some brain regions but not others can alter free will perception (7–10) while noninvasive brain stimulation can modulate experimental measures of agency and volition (4, 6, 11, 12). Functional neuroimaging can identify brain regions whose activity correlates with volition or agency in normal subjects (13, 14) or is abnormal in patients with "disorders of free will" such as functional movement disorders, psychogenic nonepileptic seizures (PNES), or catatonia (15, 16). Finally, patients with brain lesions in specific locations can experience profound disruptions in volition and agency. For example, patients with akinetic mutism lack the motivation to move or speak (17), while patients with alien limb syndrome feel that their movement is generated by someone else (18). These lesion-induced syndromes are often used as paradigmatic examples of disrupted volition and agency, respectively (15).

Despite these studies, localization of volition and agency in the human brain remains unclear. Alterations in free will perception have been reported following stimulation to a variety of different brain regions (4, 6–12) and neuroimaging correlates of free will perception have been highly heterogeneous across different studies (13, 14). Even focal brain lesions, often considered the gold standard for neuroanatomical localization (19–21), can occur in multiple different brain locations but cause similar disruptions in volition or agency (22, 23).

Lesion network mapping (Fig. 1) is a recently validated technique that identifies regions functionally connected to a lesion location, allowing one to localize symptoms even when lesions occur in different brain locations (24–28). For example, lesions that cause visual hallucinations fall within a single brain network connected to extrastriate visual cortex, lesions that cause pain fall within a network connected to the posterior insula, and lesions that cause aphasia fall within a network connected to the left inferior frontal gyrus (24). This approach has been validated for 2D approximations of 3D lesions including images of lesions from published articles (24, 26) and has lent insight into complex but poorly understood neuropsychiatric syndromes such as abnormal movements (28, 29), delusions (26), loss of consciousness (27), and criminal behavior (30). A similar approach has been applied to brain stimulation sites in different locations that relieve similar symptoms (31, 32).

Here, we use this network localization approach to determine the neuroanatomical substrate of disordered free will perception. First, we test whether lesions in different brain locations causing akinetic mutism and alien limb are part of the same functionally connected brain network. Second, we test for specificity by comparing our results to

lesions causing similar physical symptoms, but with intact perception of volition and agency. Finally, we test whether our localization of volition and agency based on focal brain lesions align with brain stimulation sites altering free will perception and neuroimaging abnormalities in psychiatric patients with disordered free will perception.

Results

Lesion network localization of disordered volition

We identified 28 cases where lesions impaired the ability to volitionally initiate movements, causing akinetic mutism or abulia (Table S1). Lesions were traced onto a standard brain atlas (Fig. 2A, Fig S1). Lesion locations were heterogeneous, including the anterior cingulate cortex (ACC; 21% cases), globus pallidus (29%), thalamus (25%), caudate (18%), and brainstem (11%).

Next, we performed lesion network mapping to determine if these lesion locations were part of a common brain network. Regions functionally connected to each lesion location were identified using a large database (n=1000) of resting state functional connectivity from normal subjects (33). Brain regions that were significantly positively or negatively correlated with each lesion location were identified (Fig. 1B) (24, 30, 32, 34). These lesion network maps were then thresholded at $T \geq 5$ (corresponding to whole brain voxelwise family-wise error (FWE) corrected $P<0.05$), binarized, and overlapped to identify brain regions significantly connected to all or most lesions causing disordered volition (Fig. 1C). While lesions occurred in different locations, all 28 lesions (100%) were part of a single brain network defined by functional connectivity to the ACC (Fig. 2B; Table S2).

To assess specificity, we compared the lesion connectivity in patients with akinetic mutism / abulia to patients with hemiparesis. Hemiparesis patients also fail to initiate voluntary movements on their paralyzed side; however, in contrast to patients with akinetic mutism or abulia, hemiparesis patients retain the urge and motivation to move (i.e. intact volition). We identified 25 lesions causing hemiparesis (35), performed lesion network mapping as above (Supplementary Fig. S2), and statistically compared the results to lesions that disrupt volition. Lesions causing disordered volition were significantly more connected to the ACC compared with lesions causing hemiparesis, among other regions (Fig. 2C; Table S3).

To illustrate that lesion locations disrupting volition are part of a common brain network, we computed functionally connectivity with our site of peak network overlap in the anterior cingulate (Fig. 2D, MNI coordinate x= 2, y= 18, z= 32) which defines a spatial network that, by definition, encompasses lesion locations disrupting volition (Figure 2E).

Lesion network localization of disordered agency

We identified 50 cases of brain lesions causing involuntary movements that patients claimed they were not responsible for generating, a clinical syndrome termed alien limb (Table S1, Fig. S3). Again, lesion locations were diverse and included the medial frontal cortices (24%), corpus callosum (22%), parietal lobes (36%), and thalamus (8%) (Fig. 3A). While the lesions themselves were spatially diverse, lesion network mapping showed that 45 of the 50 lesions (90%) fell within a single brain network defined by functional connectivity to the precuneus cortex (Fig. 3B; Table S2).

To assess specificity, we compared lesions causing alien limb to lesions causing hemichorea (Supplementary Fig. S2) (28). In hemichorea, patients have involuntary movements, similar to patients with alien limb; however patients with hemichorea continue to feel responsible for these movements (i.e. intact agency) (15). We found that connectivity to the precuneus region was specific to lesions causing alien limb compared to hemichorea (Fig. 3C, Table S3).

For illustration purposes, we computed functional connectivity with our site of peak network overlap in the precuneus (Figure 3D, MNI coordinate x= 10, y= -40, z= 50), which, by definition, defines a spatial network that encompasses lesions locations disrupting agency (Figure 3E).

Network localization of brain stimulation sites altering free will perception

To test whether our results, derived from focal brain lesions, align with results of prior brain stimulation studies, we identified 16 stimulation sites altering free will perception based on a systematic literature search (10 direct electrical stimulation, 6 TMS; Table S4). We also identified 17 control stimulation sites from the same studies that did not alter free will perception (11 direct neurosurgical stimulation, 6 TMS). Similar to brain lesions, stimulation sites altering free will perception have been reported across multiple different brain locations (Fig. 4A). However, 15/16 (94%) of these stimulation sites were part of a common functionally connected brain network that overlapped almost exactly with our volition and agency networks derived from focal brain lesions (Fig 4B). This connectivity pattern was specific for stimulation sites altering free will perception compared to stimulation sites that did not alter free will

perception (Fig. 4C). Finally, stimulation sites altering free will perception were significantly more connected to our lesion-derived region of interest for volition (see Figure 2D) and agency (see Figure 3D) compared to stimulation sites that did not disrupt free will (F $(2,30)$ = 3.69, p <0.05).

Network localization of neuroimaging abnormalities in psychiatric disorders of free will perception

Next, we tested whether our localization of volition and agency based on focal brain lesions was relevant to psychiatric "disorders of free will" such as motor conversion disorder, PNES, or catatonia. Although these patients do not have focal brain lesions, we identified neuroimaging studies that reported areas of focal atrophy or decreased function in groups of patients with these disorders (motor conversion, n=6; catatonia, n=4; PNES, n=3; Table S5). Using the neuroimaging coordinates from each study as a "lesion", we repeated the same analysis we used for lesion locations (Figure 5A). Neuroimaging coordinates from 85% of studies were functionally connected to a common brain network that aligned well with our network derived from focal brain lesions (Fig. 5B). This connectivity was specific for neuroimaging abnormalities reported in psychiatric patients with disordered free will perception compared to neuroimaging abnormalities from patients without disordered free will perception (Alzheimer's disease, n=31, Fig. 5C) (36). Neuroimaging abnormalities in psychiatric disorders of free will were significantly more connected to our lesion-derived region of interest for volition (see Figure 2D) and agency (see Figure 3D) compared to neuroimaging abnormalities from patients without disordered free will perception (F $(2, 41)$ = 10.76; p <0.001).

Discussion

Our results show that lesions that disrupt free will perception occur in different brain locations but localize to common brain networks. Specifically, we show that lesions that disrupt volition, causing akinetic mutism or abulia, are part of a common brain network defined by connectivity to the ACC. Lesions that disrupt agency, causing alien limb, are part of a common brain network defined by connectivity to the precuneus. Finally, we show that our lesion-based localization of volition and agency align well with brain stimulation sites that disrupt free will perception and neuroimaging abnormalities in psychiatric patients with disordered free will perception.

Lesions causing disordered volition localize to a distinct brain network defined by connectivity to the ACC

The heterogeneity of lesion-induced akinetic mutism and abulia has led to speculation that disordered volition is a network phenomenon (6, 22, 37). Using brain connectivity with lesion locations, we defined this network and found that it was centered in a specific part of the ACC. The ACC is thought to be involved in the motivation, planning, and control of volitional movements (5, 38) and is the chief neuroimaging correlate of volition in healthy subjects (5, 14). Surgical lesioning of the ACC for depression, OCD, or chronic pain is associated with impaired volition, although milder than in patients without these disorders who experience a stroke in this area (39–41). While it remains unknown why neurosurgical lesions lead to milder symptoms, one possibility is that the effects of a lesion are different in psychiatric patients with pre-existing dysfunction in the ACC. This is analogous to ablation of the subthalamic

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nucleus in patients with Parkinson's disease, which leads to much milder hemiballismus vs. lesions in previously normal persons (42).

Lesions causing disordered agency localize to a distinct brain network defined by connectivity to the precuneus

Lesions causing disordered agency (alien limb syndrome) occurred in a network centered in the precuneus. Our peak network overlap site was in the right precuneus, consistent with more common involvement of the left limb in alien limb syndrome in our study (56% of cases) and in prior reports (23, 43, 44). The precuneus has previously been implicated in the normal sense of agency (13, 45), as well as in self-referential processing and visuospatial and motor integration for the body (45).

Interpreting Lesion Network Localization

Our finding that heterogenous lesion locations disrupting volition or agency localize to connected brain networks is consistent with a growing number of lesion network mapping studies across a variety of neuropsychiatric symptoms (21). The interpretation is similar to traditional lesion studies, but rather than localizing lesion deficits to a brain region these studies localize deficits to a brain network. One mechanism that may explain this network localization is functional diaschisis, or remote functional effects of a lesion on anatomically intact but connected brain regions (46–49). According to this interpretation, lesion locations functionally connected to the ACC may result in remote functional effects on the ACC, disrupting volition, while lesion locations

functionally connected to the precuneus may result in remote functional effects on the precuneus, disrupting agency. Another possibility is that volition requires intact function of a network of brain regions connected to the ACC while agency requires intact function of a network of brain regions connected to the precuneus, and lesions to any of these regions can disrupt volition and agency. According to this interpretation, agency and volition are properties of the entire network, rather than one specific region within that network. These interpretations are not mutually exclusive, and further work is needed to differentiate between them.

One possible concern is that lesion network mapping biases towards finding "hub" regions (e.g. precuneus) that are connected to more regions than non-hub regions (50). However, several pieces of evidence point against this interpretation. First, previous lesion network mapping studies have often identified non-hub regions, such as extra-striate visual cortex for lesions causing peduncular hallucinosis (24). Second, our results were specific compared to lesion locations causing other symptoms which controls for any potential hub bias. Finally, the precuneus location identified in our study is actually in a "non-hub" region with relatively low global connectivity compared to other brain regions (50).

Network localization of brain stimulation locations disrupting free will perception

Similar to lesion locations causing the same symptom, different brain stimulation sites causing (or relieving) the same symptom may also localize to connected brain networks (31, 32, 51, 52). Several different brain stimulation sites have been reported to alter free will perception including the ACC (7–9), pre-SMA (53, 54), and a variety of

sites in the lateral parietal cortex (10, 11, 55–57). Unlike our lesion cases, we did not

separate brain stimulation sites into altered volition versus agency due to a much lower N

(14 versus 78) and the fact that many stimulation effects were an ambiguous combination

of the two. Despite this heterogeneity, these stimulation sites shared functional

connectivity to a common brain network. More importantly, this network aligned with

our network for free will perception derived from focal brain lesions. Convergent

findings across two different causal sources of information (brain lesions and brain

stimulation) increases confidence in the current results.

Preliminary extension of network localization to neuroimaging abnormalities in

psychiatric patients.

Many neuropsychiatric diseases without overt brain lesions are conceptualized as

disorders of free will. These include functional movement disorders, PNES, and

catatonia (15). Our finding that neuroimaging abnormalities in these other disorders are

part of the same brain network as focal brain lesions that disrupt volition and agency

suggests a common substrate for free will perception. Future studies can address whether

neuroimaging abnormalities in other disorders of free will, such as delusions of control

and passivity symptoms in schizophrenia, show similar network localization. However,

these results should be taken with caution: unlike lesion network mapping itself, which

has been applied and validated across multiple lesion-induced symptoms (24, 26–29, 34),

this is the first time this approach has been applied to neuroimaging abnormalities from

groups of psychiatric patients. Specifically, although we treated these reported imaging

abnormalities on structural MRI, FDG-PET, and SPECT as "lesions" in our analysis, the

actual dysfunction in these regions is likely to be far more complex. The current results

suggest that conceptualizing these abnormalities as functional "lesions" may have value;

however testing in other symptoms with more established localization is needed.

Limitations related to lesion network mapping

There are important limitations of the lesion network mapping technique, many of

which have been addressed previously (24, 26, 30). First, accuracy of manual lesion

tracing is limited by the quality of published images, and we used 2D lesions based on

published images, which may not fully capture the spatial extent of 3D lesions.

However, our prior studies have shown that the connectivity of 2D representations of 3D

lesions is highly similar to the 3D lesion itself (spatial correlation coefficients >0.9) (24,

26). Moreover, any errors in lesion tracing should bias us against finding consistent

network localization across lesions.

Another concern is that lesion network mapping results may depend on the specific

connectome dataset used for the analysis. We have previously shown that results do not

change when using an age-matched or disease-specific connectome (24, 31). Similarly,

results do not change when using alternative connectome processing strategies (24, 31).

Finally, we used a large (n=1000) normative connectome to determine functional

connectivity between different parts of the brain. While this provides a highly accurate

representation of group level connectivity, it is possible that individual patient differences

in connectivity would lead to different results. However, obtaining functional

connectivity imaging from patients prior to the occurrence of a brain lesion is not

practical, and functional connectivity with the lesion location can't be computed using

data obtained from patients after the lesion has occurred (that tissue is now dead), leaving a large normative connectome as the best practical option.

Because our analysis uses functional connectivity, we cannot determine whether the current results are driven by monosynaptic or polysynaptic connections, nor the potential directionality of such connections. Moreover, because we use a normative connectome, not functional neuroimaging data from patients themselves, direct physiological effects of the lesions are not measured.

Limitations related to defining disordered agency and volition

An important set of limitations relates to our definition of disordered volition and agency. First, we identified cases of akinetic mutism/abulia and alien limb retrospectively, without standardized patient assessment or recording of symptoms. Important differences between patients were not taken into account, such as the severity of abulia vs. akinetic mutism, or the specific limb affected by alien limb symptoms. This heterogeneity broadens the applicability of the present findings, but increases that chance that more subtle findings may have been missed. Second, it is possible that alien limb and akinetic mutism, clinical syndromes classically used to define abnormal free will perception (15), do not map onto the neural processes we normally associate with "free will" in healthy subjects. For example, one could argue that denying agency in patients with alien limb and involuntary movements is not a disorder of agency, but that continuing to experience agency for involuntary movements in patients with hemichorea is. Similarly, the clinical syndrome of akinetic mutism could result from impaired motivation to make a desired movement, impaired selection of a movement one a desire

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is made, and/or from impaired initiation of a desired movement. Our approach cannot differentiate between these impairments, but rather shows common network localization independent of this distinction.

Finally, our study was focused on patients with disorders of free will for movements. However, free will is commonly discussed as it relates to social, legal, and moral responsibility for decisions, not just movement (3, 4). It remains unknown whether the network of brain regions we identify as related to free will for movements is the same as those important for moral decision-making (58–60), as prior studies have suggested important differences (30).

Materials and Methods

Patient cases from the literature

To identify patients with disordered volition caused by brain lesions, we searched Pubmed for articles with human subjects written in English using the search terms ("akinetic mutism" or abulia) and (mri or ct or neuroimaging) and (stroke or hemorrhage or bleed or lesion). 80 studies were identified. Inclusion criteria included 1) Documentation of diminished volitional movements (defined as the presence of spontaneous movements and/or speech in the absence of movement to commands); 2) Focal brain injury due to ischemic or hemorrhagic stroke; and 3) Published structural image (CT or MRI) of high enough quality to be traced onto a standardized brain atlas. 28 cases fulfilled these criteria and were included. A Pubmed search was performed to identify patients with alien limb syndrome using the search terms ("alien limb" or "alien hand"). 266 studies were identified. Inclusion required 1) Documentation of movements that a patient claimed they were not responsible for; 2) Focal brain lesion due

to an ischemic or hemorrhagic stroke; and 3) Published structural image (CT or MRI) of sufficient image quality to trace onto a standardized brain template. 50 cases met inclusion criteria and were included in the study.

Lesion localization

Published images were traced by hand onto a standardized brain atlas (2x2x2 MNI space) using FSL as in prior work (24, 26–29). All lesions shown in the original publication were traced for each patient.

Lesion network mapping

Our group recently developed a technique termed lesion network mapping that identifies brain regions functionally connected to lesion locations causing a given neuropsychiatric symptom (24, 26–29, 32, 34). This technique avoids the need to perform functional brain imaging on the patients themselves and has been validated across many different neurological syndromes. Briefly, traced lesions were used as individual seeds in a resting-state connectivity analysis using data from obtained from 1000 healthy subjects (33). Functional connectivity to each lesion was determined by calculating the correlated time-course between each lesion location and every other brain voxel using the resting state data from each individual normal control, as described in our prior studies using this connectome (32, 34). These correlations for all 1000 subjects were then combined to calculate a T-score value for every individual voxel. Voxels were thresholded at $T > +/- 5$ in order to create a binarized map of significantly functionally connected regions to each patient's lesion site (whole-brain voxel-wise FWE corrected $p < 0.05$; uncorrected $p < 10^{-6}$). Finally, maps from each of the patients were combined to

form the lesion network mapping overlap for the group, showing the number of patients with lesions functionally connected with each individual voxel.

Comparison to lesions causing similar neurological syndromes

Lesion network mapping results of lesions causing akinetic mutism or abulia were compared with lesions causing hemiparesis, which differed according to whether volition was absent (akinetic mutism / abulia) or intact (hemiparesis). 25 lesions causing hemiparesis were obtained from a previously published study (35). Lesion network mapping results of lesions causing alien limb were compared with lesions causing hemichorea, which differed according to whether agency was absent (alien limb) or intact (hemichorea). 39 lesions causing hemichorea were obtained from a previously published study (28). Group differences in lesion network connectivity were calculated using voxel-wise, two-sample t-tests implemented in Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The search volume included the whole brain. In all analyses, voxelwise FWE-corrected P-values less than 0.05 were considered significant.

Network localization of brain stimulation locations disrupting free will perception

To identify studies where free will perception was disrupted through either direct electrical stimulation during neurosurgical cases, or from focal noninvasive brain stimulation using transcranial magnetic stimulation (TMS), we searched Pubmed for articles with human subjects written in English using the search terms ("direct electrical stimulation" or "noninvasive brain stimulation" or "transcranial magnetic stimulation") and ("volition" or "agency"). 119 studies were identified. We limited studies to TMS

and excluded tDCS studies due to the poor neuroanatomical specificity using tDCS. Inclusion required either coordinates for the stimulation location in a standardized brain space, or an image of the stimulation location that could be manually traced onto a standardized brain template. We also included active control stimulation sites from these same studies that did not alter free will perception for comparison.

4mm spherical seeds were created at each stimulation site that did (n=16) or did not (n=17) alter free will perception. Functional connectivity with each seed to voxels in the rest of the brain was computed as above across 1000 normal subjects and analyzed as above to determine if these different stimulation locations disrupting free will perception were part of the same functionally connected brain network. Group differences in network connectivity between stimulation locations that did vs. did not alter free will were calculated using voxel-wise, two-sample t-tests implemented in SPM12 as above using a FWE-corrected P-value less than 0.05.

To test the relationship between stimulation sites that disrupt free will and lesions that disrupt free will we generated 8mm seed regions centered on the peak lesion network overlap site for akinetic mutism (MNI coordinate x= 2, y= 18, z= 32) and alien limb (MNI coordinate x= 10, y= -40, z= 50). By definition, the functional connectivity networks derived from these seeds encompass the topographic distribution of lesions that disrupt volition or agency, respectively. The functional correlation in BOLD fMRI signal was measured between stimulation sites and each ROI across the n=1000 subject functional connectome. Correlation values were normalized using a Fisher's *r to z* transformation. A multivariate analysis of variance (manova) was performed with

connectivity strength to the akinetic mutism and alien limb ROI's as dependent variables, and free will effect (disrupted vs. not disrupted) as the independent variable.

Network localization of neuroimaging findings in psychiatric disorders of free will

We included three psychiatric disorders of free will perception: functional movement disorders, psychogenic non-epileptic seizures (PNES), and catatonia. We included these disorders because all three involved abnormal free will perception for movements. A Pubmed search was performed using the search terms ("psychogenic nonepileptic seizures" or "conversion disorder" or "functional neurological disorder" or "catatonia") and (mri or spect or PET), identifying 319 studies. Neuroimaging studies that compared patients to healthy control subjects and utilized PET, SPECT or structural MRI with either whole-brain cortical thickness or voxel-based morphometry (VBM) analyses were included. PET/SPECT studies were limited to those focused on blood flow or metabolism.

In each study, coordinates for functional "lesions" were extracted, defined as atrophy or hypo-activity on functional neuroimaging (at baseline or with volitional movement) in patients with disordered free will vs. control patients. For each individual study, we created 4mm seeds at all reported coordinates and added these together to create a single, combined seed for each study (Fig. 5A), similar to other techniques for coordinate-based neuroimaging analyses (61, 62). We then treated this combined seed for each study as a "lesion", and performed an identical procedure as our "lesion network mapping" to determine whether there was common network localization across these different studies.

To test the specificity of our network localization to regions involved in free will, we compared our results with neuroimaging abnormalities in 31 studies of patients with Alzheimer's disease (36). Group differences in network connectivity were calculated using voxel-wise, two-sample t-tests implemented in SPM12 as above using a FWE-corrected P-value less than 0.05.

To test the relationship between neuroimaging abnormalities in psychiatric disorders of free will and lesions that disrupt free will, the functional correlation in BOLD fMRI signal was measured between the locations of neuroimaging abnormalities and the previously defined alien limb and akinetic mutism ROI's across the n=1000 subject functional connectome. Correlation values were normalized using a Fisher's *r to z* transformation. A multivariate analysis of variance (manova) was performed with connectivity strength to the akinetic mutism and alien limb ROI's as dependent variables, and psychiatric disorders free will vs. Alzheimer's disease as the independent variable.

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Figure Legends

Fig. 1. Lesion Network Mapping Technique.

(A) Three representative lesions causing akinetic mutism or abulia (disordered volition).

(B) Network of regions functionally connected to each lesion location across a large

(n=1000) resting state functional connectivity data-set. **(C)** Lesion network overlap map

showing regions connected to all or most lesion locations.

Fig. 2. Lesion network localization of disordered volition.

(A) Five representative lesions (of 28 total) causing akinetic mutism, demonstrating

heterogeneity of lesion location. **(B)** Percentage of lesion locations functionally

connected to each brain voxel. **(C)** T-test comparing functional connectivity of lesions

causing akinetic mutism vs. lesions causing hemiparesis (voxel-wise FWE corrected $p <$

0.05). **(D)** Region of interest in the anterior cingulate centered on our peak site of lesion

network overlap from **B**. **(E)** Functional connectivity with this region of interest defines

a brain network (blue) that encompasses heterogeneous lesion locations disrupting

volition (red).

Fig. 3: Lesion network localization of disordered agency.

A) Five representative lesions (of 50 total) causing alien limb syndrome, demonstrating

heterogeneity of lesion location. **(B)** Percentage of lesion locations functionally

connected to each brain voxel **(C)** T-test comparing functional connectivity of lesions

causing alien limb vs. lesions causing hemichorea (voxel-wise FWE corrected p < 0.05).

(D) Region of interest in the precuneus centered on our peak site of lesion network

overlap from **B**. **(E)** Functional connectivity with this region of interest defines a brain

network (blue) that encompasses heterogeneous lesion locations disrupting agency (red).

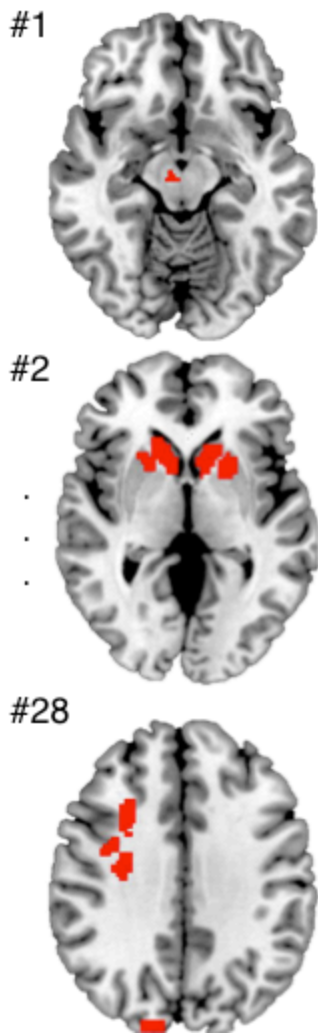**Figure 4: Network Localization of stimulation locations altering free will perception.**

(A) Four representative brain stimulation sites (of 16 total) that altered free will

perception, demonstrating heterogeneity in stimulation location. **(B)** Percentage of

stimulation sites altering free will perception functionally connected to each brain voxel.

(C) T-Test comparing connectivity of stimulation sites that did vs. did not alter free will

perception. Results in **B** and **C** are overlaid on the network of voxels connected to our

combined volition and agency ROIs derived from focal brain lesions (blue).

Fig. 5: Network localization of neuroimaging abnormalities in psychiatric disorders
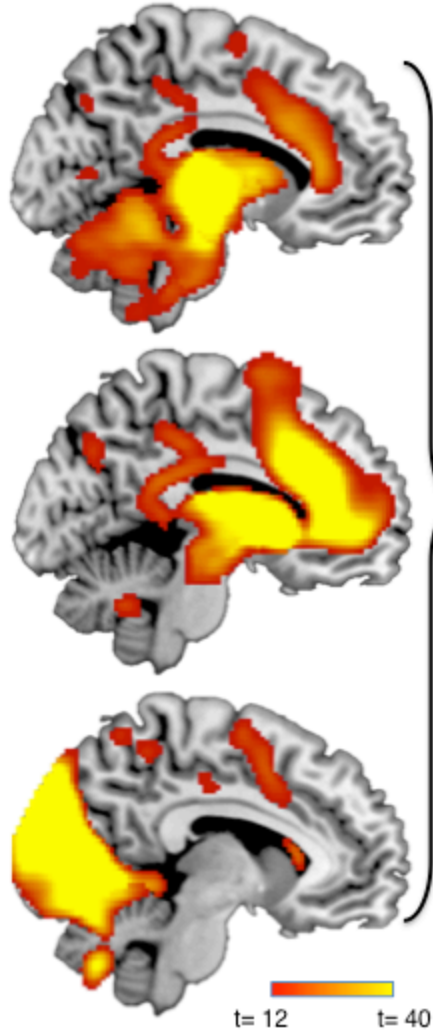
of free will perception.

A.) Coordinates from 5 representative neuroimaging studies (of 13 total) reporting

abnormalities in patients with psychiatric disorders of free will perception **B.)** Percentage

of studies whose coordinates were functionally connected to each brain voxel. **C)** T-Test

comparing connectivity of coordinates from psychiatric disorders of free will with

coordinates from a control disorder not associated with abnormalities in free will.

Results in **B** and **C** are overlaid on a map of voxels connected to our combined volition

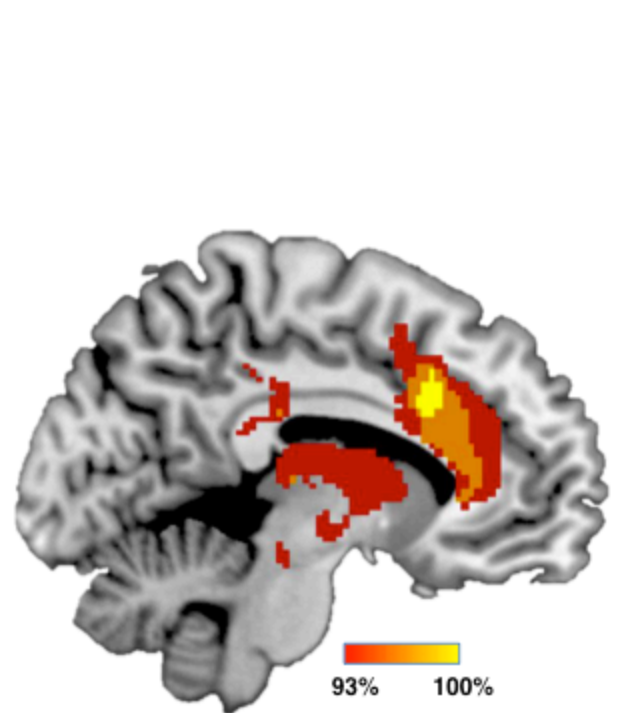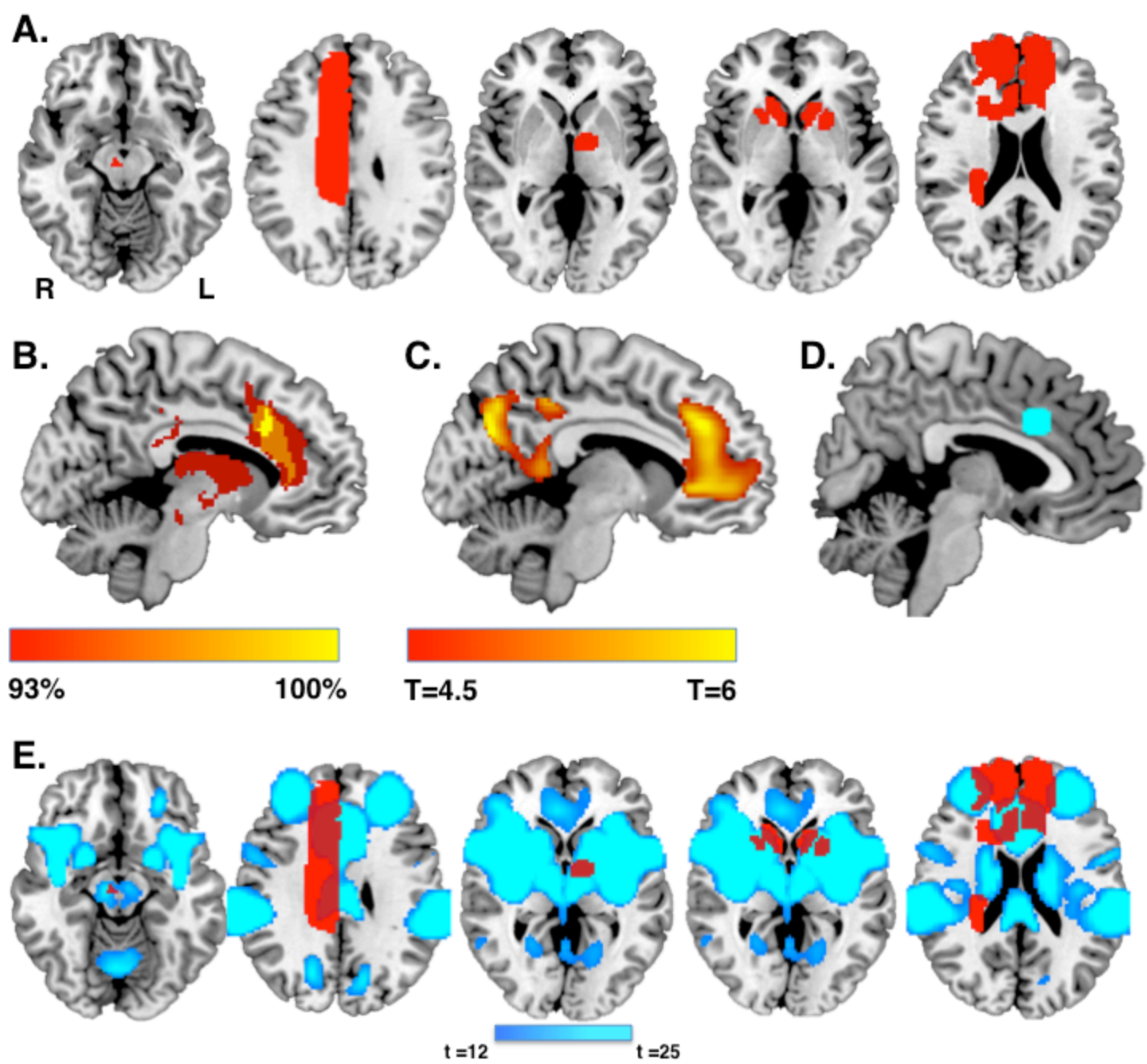and agency ROIs derived from focal brain lesions (blue).
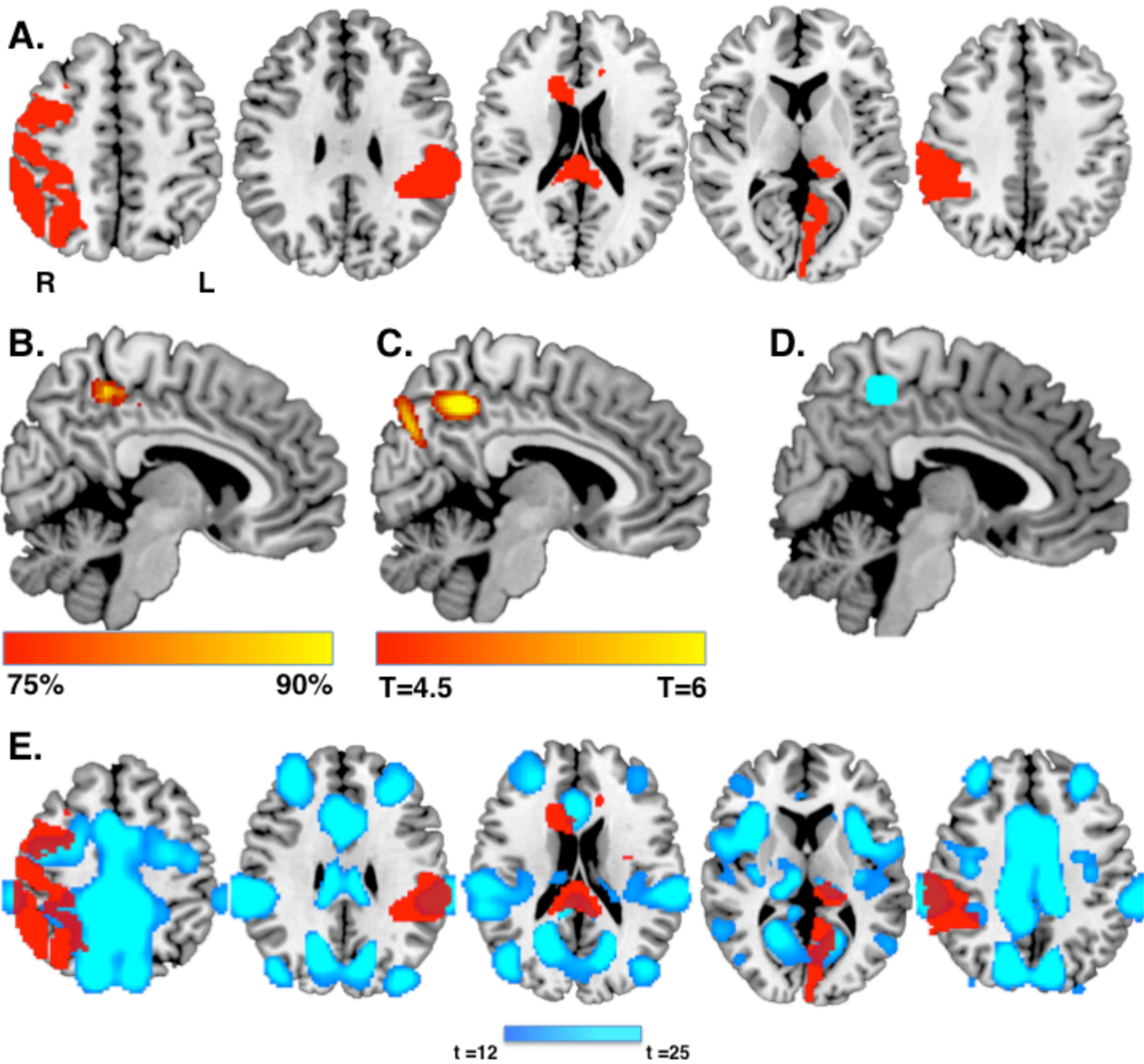
A. <u>Lesion</u>

#1

#2

.
.
.

#28

B. <u>Connectivity</u>

t= 12   t= 40

C. <u>Overlap</u>

93%   100%

A.

R   L

B.   C.   D.

93%   100%   T=4.5   T=6

E.

t =12   t =25

A.

R   L

B.   **C.**   **D.**

75%   90%

T=4.5   T=6

E.

t =12   t =25

A.

R

B.

69%   100%

C.

T=5.5   T=6.5

A.

R   L

C.

77%   92%

T=5   T=6
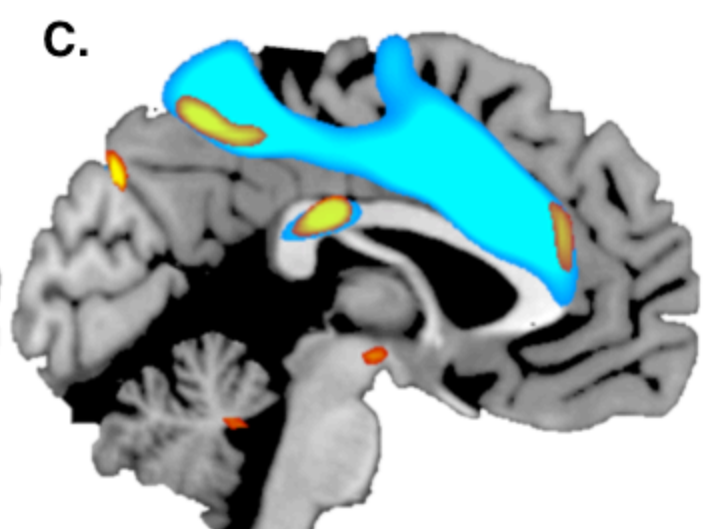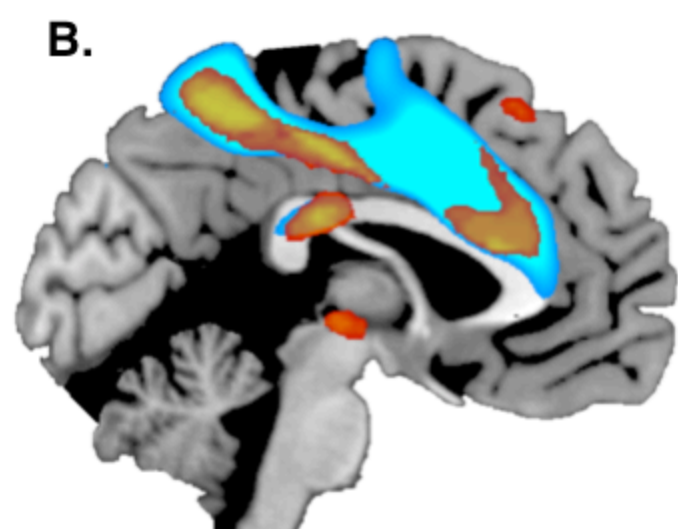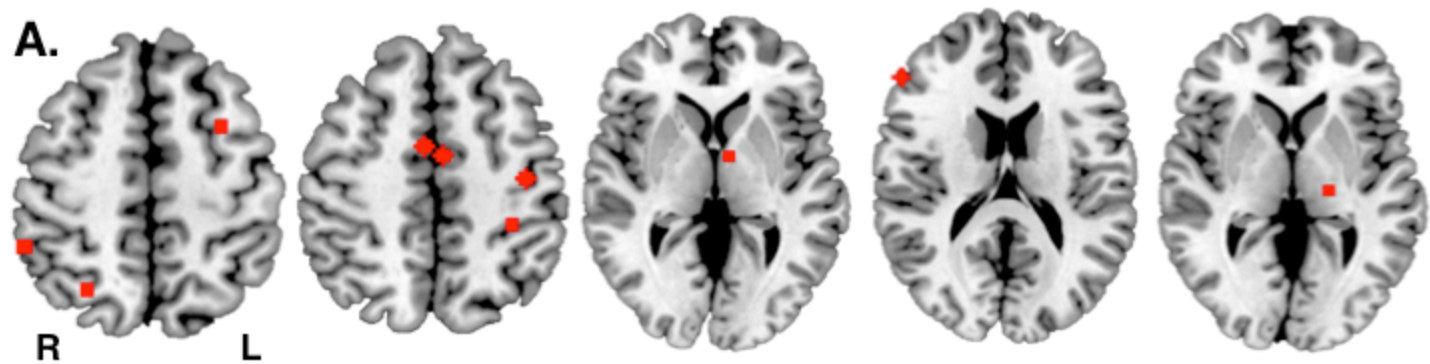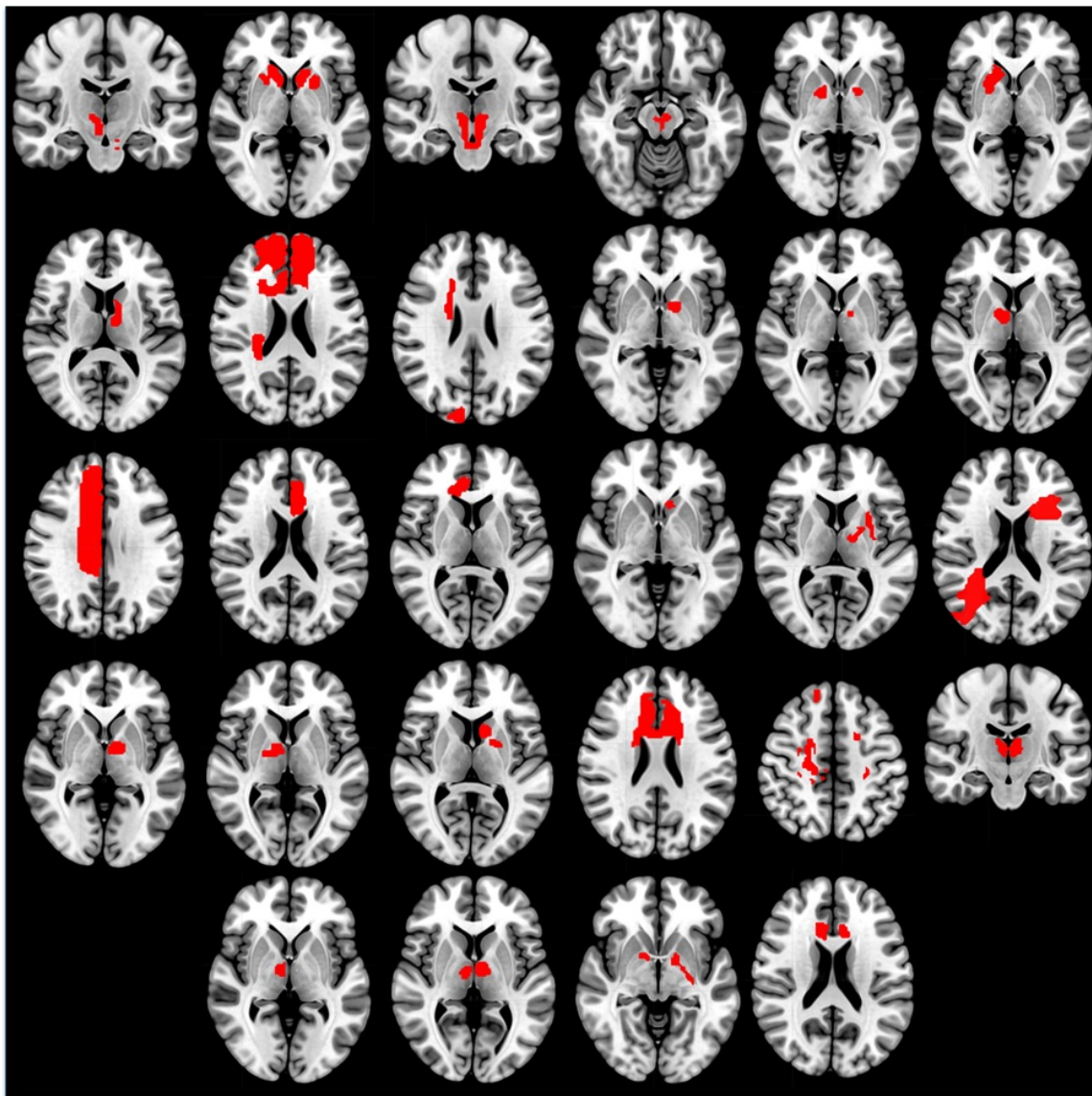
Fig. S1. Lesions causing disordered volition.
28 lesions causing either akinetic mutism or abulia were mapped onto a standardized brain atlas.
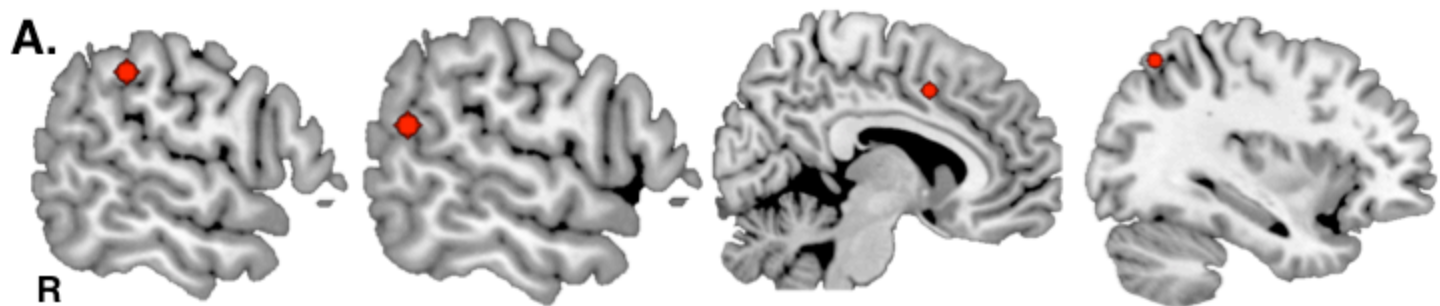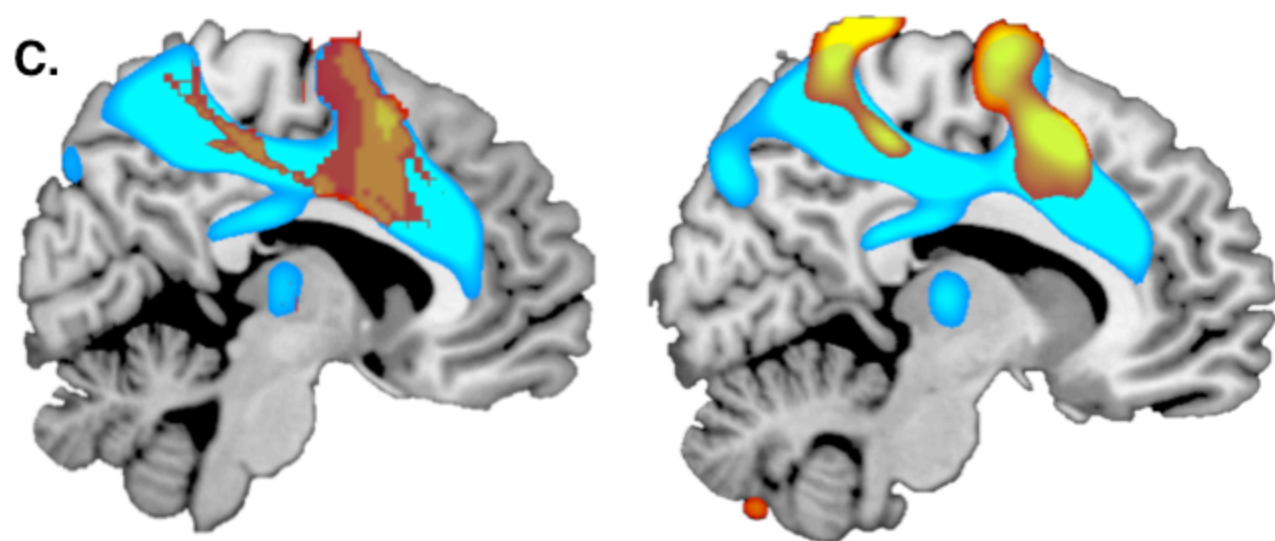
A. Hemiparesis

B. Hemichorea

80%   100%

Fig. S2 : Lesion network overlap for control syndromes. Lesion network overlap results for hemiparesis (**A**) and hemichorea (**B**). See Laganiere et al, 2016, for further details on hemichorea results.

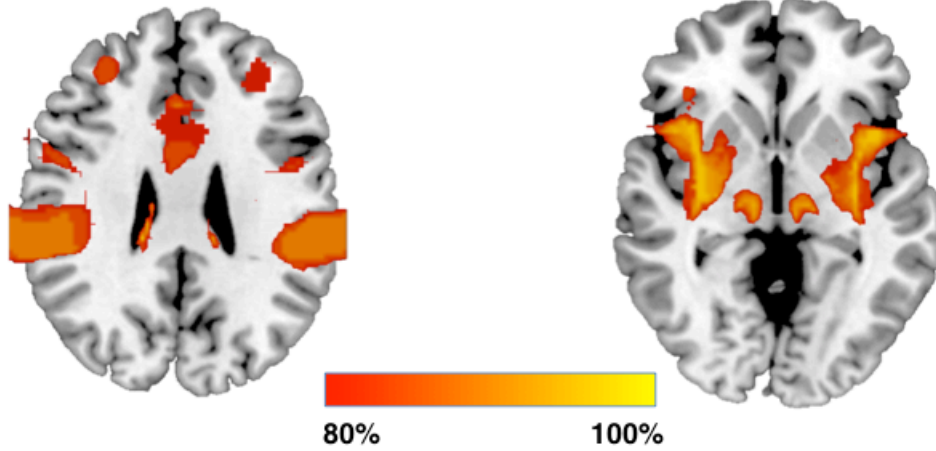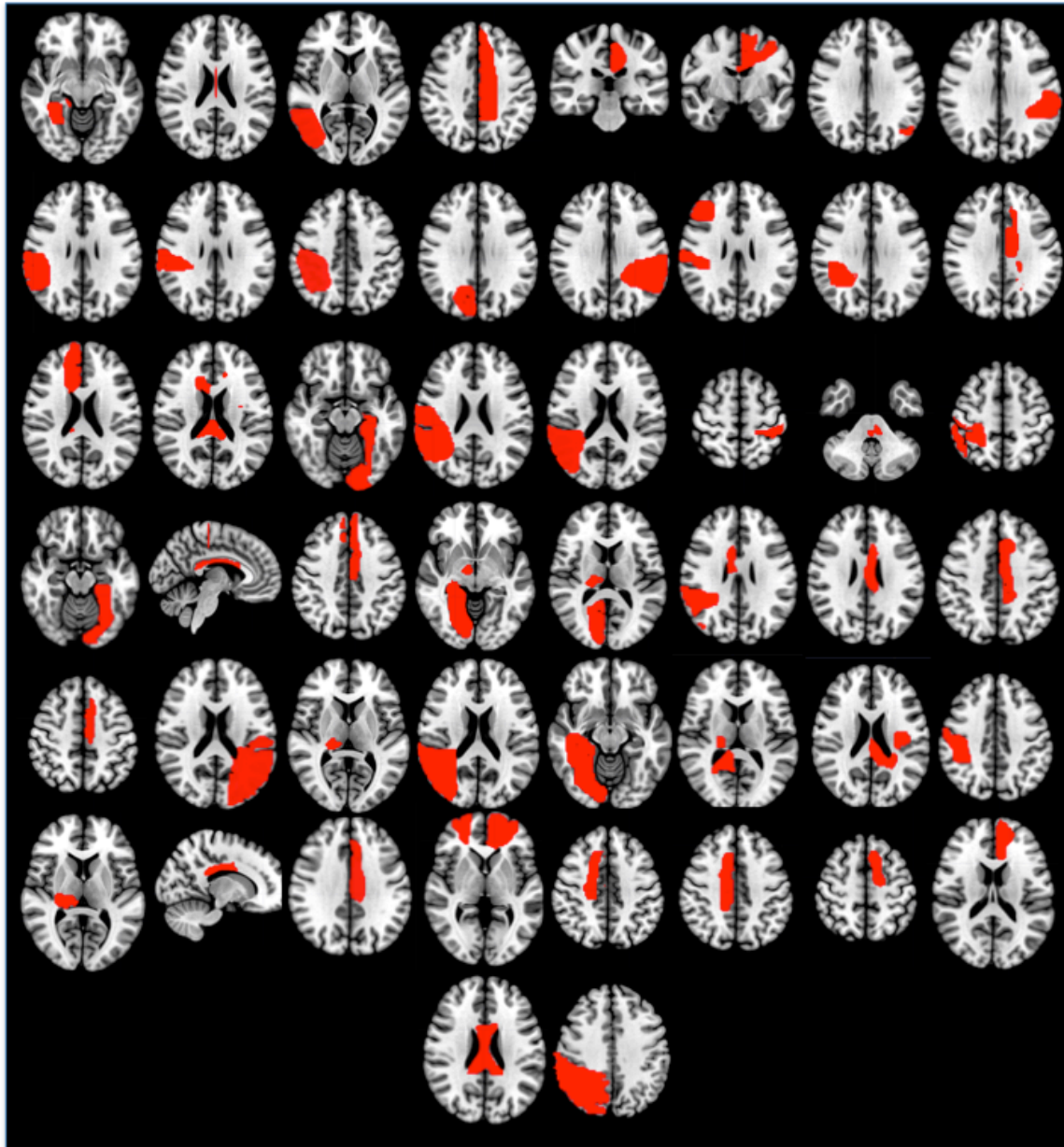**Fig. S3. Lesions causing disordered agency.**
50 lesions causing alien limb syndrome were mapped onto a standardized brain atlas.

Table S1. Akinetic Mutism and Alien Limb studies

Reference	Lesion Etiology	Patient Age
Akinetic Mutism		
Alexander et al. 2001(1)	Stroke	36
Fukuoka et al. 2012(2)	Stroke	81
Hochman et al. 1985(3)	Stroke	69
Kaphan et al. 2014(4)	Toxic ischemia from carbon monoxide	18
Krolak-Salmon et al. 2000(5)	Stroke	53
Kumral et al. 1999(6)	Stroke and hemorrhage	2 cases (N/A)
Kumral et al. 2002(7)	Stroke	N/A
Lim et al. 2007(8)	Stroke	72
Madureira et al 1999(9)	Stroke	3 cases (64,70, 64)
Nagaratnam et al. 2004(10)	Stroke	6 cases (77, 75,38, 72, 79,73)
Naito et al. 2010(11)	Stroke (septic emboli)	3 cases (64, 65,65)
Nicolai et al. 2001(12)	Stroke	70
Okamoto et al. 2004(13)	Stroke	79
Pluchon et al. 2011(14)	Stroke	6
Shetty et al. 2009(15)	Stroke	77
Siegel et al. 2014(16)	Stroke	38
van Son et al. 2014(17)	Stroke	55
Yang et al. 2007(18)	Stroke	86
Alien Limb		
Amalnath et al. 2013(19)	Stroke	45
Ay et al. 1998(20)	Stroke	81
Bartolo et al. 2011(21)	Stroke	61
Biran et al. 2006(22)	Stroke	56
Brainin et al. 2008(23)	Hemorrhage, tumour resection	2 cases (53, 57)
Chan et al. 1996(24)	Stroke	54
Coulthard et al. 2007(25)	Stroke	2 cases (75, 63)
Della Sala et al. 1991(26)	Subarachnoid hemorrhage	56
Dolado et al. 1995(27)	Stroke	80
Espinosa et al. 2006(28)	Stroke	47
Geschwind et al. 1995(29)	Stroke	68
Gilk et al. 2008(30)	Stroke	55
Giroud et al. 1995(31)	Stroke	62
Goldberg et al. 1981(32)	Stroke	2 cases (63, 76)
Goldberg et al. 1990(33)	Stroke	53
Graff-Radford et al. 2013(34)	Stroke	9 cases; (average age 65)

Groom et al. 1999(35)	Stroke	79
Hanakita et al. 1991(36)	Stroke	43
Kessler et al. 2009(37)	Stroke	57
Kim et al. 2010(38)	Stroke	83
Kim et al. 2014(39)	Stroke	49
Lin et al. 2007(40)	Stroke	67
Marey-Lopez et al. 2002(41)	Stroke	64
Marti-Fabregas et al. 2000(42)	Stroke	81
McNabb et al. 1988(43)	Stroke	75
Muangpaisan et al. 2005(44)	Stroke	76
Nowak el al. 2014(45)	Stroke	2 cases (54, 71)
Panda 2010(46)	Stroke	68
Pappalardo et al. 2004(47)	Stroke	60
Park et al. 2012(48)	Stroke	2 cases (72, 47)
Rafiei et al. 2009(49)	Hemorrhage	78
Sabrie et al. 2015(50)	Aneurysm/subarachnoid hemorrhage	25
Serrano-Vincente et al. 2015(51)	Stroke	65
Spector et al. 2009(52)	Stroke	78
Ventura et al. 1995(53)	Hemorrhage	68
Yamaguchi et al. 2006(54)	Stroke	86
Yuan et al. 2011(55)	Stroke	71

Table S2: Lesion network overlap of disordered volition and agency

Voxels	Overlap	X	Y	Z	Region
Akinetic Mutism					
6126	28/28	-38	12	-4	Left Anterior Insula, basal ganglia, thalamus, midbrain
3352	28/28	2	18	32	Anterior Cingulate Cortex, pre-supplementary motor area
429	27/28	-32	46	16	Left Middle frontal gyrus
215	27/28	8	-26	26	Posterior cingulate cortex
59	26/28	34	40	18	Right Middle Frontal Gyrus
20	26/28	46	-22	4	Right Superior Frontal Gyrus
Alien Limb					
612	45/50	10	-40	50	Precuneus
386	43/50	-14	-42	48	Precuneus
116	40/50	20	-70	36	Precuneus
52	43/50	14	-26	6	Right thalamus
20	39/50	-14	-76	40	Left Superior Parietal Lobe
19	38/50	4	10	24	Mid-Cingulate Cortex

Table S3: Specificity of lesion network localization for disordered agency and volition

Voxels	Max t-value	X	Y	Z	Region
Akinetic Mutism > Hemiparesis					
12291	7.05	-20	20	34	Paracingulate / Superior Frontal Gyrus
2648	6.2	-10	-70	30	Precuneus
233	5.38	54	-48	-40	Cerebellum
160	5.08	-52	-46	-42	Cerebellum
Alien Limb > Hemichorea					
2519	7.14	2	-50	48	Precuneus

Table S4: Studies of brain stimulation that disrupts free will perception

Reference	Brain Stimulation Modality	Stimulation sites	Sample Size
Desmurget et al, 2009 (56)	Direct electrical stimulation	Disrupted free will =9, control =10	N=7
Kremer et al, 2001 (57)	Direct electrical stimulation	Disrupted free will =1, control =2	N=1
Moore et al, 2010 (58)	TMS	Disrupted free will =1, control =1	N=10
Lau et al 2007 (59)	TMS	Disrupted free will =1, control =1	N=10
Kammers et al 2009 (60)	TMS	Disrupted free will =1	N=14
Tsakiris et al, 2008 (61)	TMS	Disrupted free will =1, control =1	N=10
Ritterband-Rosenbaum et al, 2014 (62)	TMS	Disrupted free will =1, control =1	N=12
MacDonald et al, 2003 (63)	TMS	Disrupted free will =1, control =1	N=12

TMS = transcranial magnetic stimulation

Table S5. Neuropsychiatric disorders of free will studies

Reference	Diagnosis	Sample size	Imaging Modality
Arthuis et al. 2015(64)	PNES	Patients = 16, Controls = 16	FDG-PET
Labate et al. 2012(65)	PNES	Patients = 20, Controls = 40	MRI (VBM)
Ristic et al. 2015(66)	PNES	Patients = 37, Controls = 37	MRI (Cortical Thickness)
Schrag et al. 2013(67)	Functional dystonia	Patients = 6, DYT1 Dystonia = 5, Controls = 6	FDG-PET
Voon et al. 2011(68)	Functional movement disorder	Patients = 11, Controls = 11	fMRI
Marshall et al. 1997(69)	Functional weakness	Patients = 1	SPECT (rCBF)
Spence et al. 2000(70)	Functional weakness	Patients = 2, Feigners = 2, Controls = 6	FDG-PET
Stone et al. 2007(71)	Functional weakness	Patients = 4, Controls = 4	fMRI
Vuilleimer et al. 2001(72)	Functional weakness	Patients = 7	SPECT (rCBF)
Payoux et al. 2004(73)	Akinetic schizophrenia	Patients = 6, Controls = 6	fMRI
Scheuerecker et al. 2009(74)	Catatonic schizophrenia	Patients = 12, Controls = 12	fMRI
Walther et al. 2011(75)	Akinetic Schizophrenia	Patients = 11, Controls = 14	MRI (Arterial spin labelling)

Legend: PNES = psychogenic non-epileptic seizure, VBM = voxel-based morphometry

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