A fronto-insular-parietal network for the sense of body ownership

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Article

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Abstract

Neuropsychological disturbances in the sense of limb ownership (DSO) provide a unique opportunity to study the neurocognitive basis of the sense of body ownership. Previous small sample studies focused on discrete cortical lesions and modular accounts, which cannot explain the modulations of DSO by multisensory, affective and cognitive manipulations. We tested the novel hypothesis that DSO would be associated not only with discrete cortical lesions, but also with disconnections of frontoparietal and fronto-insular white-matter tracts, supporting functional networks for multisensory integration and salience monitoring. To overcome the aforementioned methodological limitations, we drew on an advanced, probabilistic lesion-analysis and Bayesian statistics approach and tested this hypothesis in 49 right-hemisphere patients. Our results reveal that, as predicted, DSO is associated with lesions and disconnections of a fronto-insular-parietal network, suggesting that the sense of body ownership involves the convergence between bottom-up processes of multisensory integration and top-down control and monitoring of sensory salience.

Introduction

A fundamental aspect of self-consciousness is the sense of body ownership (SBO), or the experience of one's physical body as belonging to the unitary self\(^1\). The SBO is considered distinct from the attribution of body parts to a conceptual self\(^2\) typically studied by projecting one's body parts as images, or on video displays and testing their self-recognition in extrapersonal space (e.g.\(^3\)). A different tradition of studies has investigated the SBO as a more intuitive and less doxastic sense of the body\(^4,5\) using experimental manipulations to identify the mechanisms by which sensations are combined to give rise to the SBO in different temporal, spatial and affective conditions\(^5-7\). In this tradition, the SBO is regarded less as a fixed mental representation of the body in the brain and more as a dynamic process of multisensory integration, subject to both learned top-down factors, and bottom-up sensory signals. Consistently with these insights, functional neuroimaging studies have shown that the SBO is supported by a network of multimodal areas, composed of premotor, temporoparietal, and occipital areas, as well as the insular cortex (\(^7,8\) for reviews). The functional role of the insula in the SBO seems to relate both to its contribution to the salience network of the brain\(^9\) and to its fundamental role in the central processing of interoceptive signals from the body\(^10\). Indeed, several studies have shown that the degree to which certain sensations are integrated to give rise to the SBO relies on their salience and reliability in given spatial, temporal and even social contexts\(^11,12\). Moreover, it has been increasingly understood that the SBO not only involves the integration of exteroceptive modalities such as vision and touch, but also interoceptive modalities such as cardiac and respiratory systems, as well as affective touch\(^13,14\). Finally, in accordance to more general computational insights about dynamic brain functions, the SBO has been recently understood as the consequence of probabilistic inferences of the most likely cause of one's multisensory experience in theoretical\(^11,12\), empirical\(^15\) and computational\(^16\) investigations.
Despite progress in understanding the SBO through such experimental and computational efforts, it remains difficult to tease apart the phenomenally elusive components of body ownership. It seems even harder to create convincing and lasting conditions of subjective body disownership in the lab\textsuperscript{4,17}. By contrast, neurological patients with symptoms such as asomatognosia (lack of recognition regarding the existence or ownership of one's limbs;\textsuperscript{18}) show a clear and long-lasting, subjective experience of body disownership, denying ownership of their affected body parts for days, weeks or months\textsuperscript{19}. Sometimes this denial is accompanied by delusions about the affected arm (somatoparaphrenia;\textsuperscript{20}) and it may take several clinical forms (\textsuperscript{19}; see\textsuperscript{18,21} for reviews). The term ‘disturbed sensation of limb ownership’ (DSO;\textsuperscript{19,22,23}) captures any behavioural manifestation that involves abnormal feelings and beliefs regarding the recognition, ownership and sense of belonging of one's limbs in the first person and in peripersonal space.

DSO has been studied primarily via small samples and without control for concurrent, neuropsychological symptoms in standard symptom-lesion mapping analyses\textsuperscript{24,25} (see\textsuperscript{18,21,26} for discussions). Furthermore, these studies focused on the identification of discreet cortical lesions to areas such as the supramarginal gyrus, or the ventral prefrontal cortex\textsuperscript{27} or the insula\textsuperscript{22}, thereby encouraging modular explanations of SBO. However, more recent studies show that symptoms cannot be explained by discrete lesions as they are subject to modulation by multisensory, affective and cognitive manipulations\textsuperscript{13,21,23,28−31} and linked to damage to wider, but currently underspecified, cortical networks and white matter tracks\textsuperscript{24−27}. These observations are consistent with the novel hypothesis we aim to test in the present study, that DSO is not the result of damage to discreet cortical areas, but rather a functional disconnection of widely distributed networks involved in context-dependent, multisensory integration and belief updating processes. This proposal draws on the aforementioned theories of the SBO as a probabilistic, inferential process of belief updating regarding the causes of sensations, based on their relative salience or reliability in given spatial, multisensory and social contexts\textsuperscript{11,12,15} and our recent understanding of the disconnections underlying another right hemisphere syndrome, namely anosognosia for hemiplegia\textsuperscript{32,33}.

Accordingly, we predicted that DSO would be associated with damage not only to discrete frontal, parietal and insular cortical regions, but also with disconnections of fronto-parietal (superior longitudinal fasciculus) and fronto-insular white matter tracts supporting functional networks for multisensory integration and salience monitoring\textsuperscript{32}. To study this hypothesis and overcome the aforementioned methodological limitations in the field, we drew on a relatively large cohort of right hemisphere stroke patients (N = 174), from which we selected patients with a reliable diagnosis of DSO (n = 23; DSO + group) and compared them to a group of control patients, matched on all key demographic and clinical variables, apart from a complete absence of DSO (n = 26; DSO- group; see Table 1). To our knowledge, this is the largest sample of patients with DSO ever studied. In addition, we used an advanced lesion analysis method (BCBtoolkit,\textsuperscript{34}), which generates a probabilistic map of disconnections from each patient’s brain lesion to identify the disconnections that are associated with given neuropsychological
deficits at the group level, and has been successfully used to examine the brain disconnections implicated in several other neuropsychological disorders\textsuperscript{32,35}. Finally, we used advanced Bayesian statistics to identify the lesions associated with DSO, over and above explaining the clinical data, and applied cluster analyses on the resultant lesion patterns, to identify which network of structures form the neuroanatomical basis of DSO symptoms.

**Table 1.** For DSO and control groups, mean and $\pm$ standard deviation of demographic and clinical variables, neurological and neuropsychological assessments are reported. Bayes Factors (BF\textsubscript{10}) were calculated, with BF\textsubscript{10} > 3 = alternative hypothesis (there are differences between the groups); a BF\textsubscript{10} < 1/3 = null hypothesis (no differences between groups); results within 3 and 1/3 are inconclusive. All comparisons show no differences between the two groups (BF\textsubscript{10} < 1/3, acceptance of the null hypothesis), with one exception (indicated in italic within the table) in the Interval since lesion onset in days. In this latter case, BF\textsubscript{10} does not allow to accept the null hypothesis, but it represents an anecdotal evidence towards the null hypothesis\textsuperscript{36}. H1 = the scores between the two groups are different; H0 = the scores between the two groups are equal.

<table>
<thead>
<tr>
<th></th>
<th>DSO (N=23)</th>
<th>Controls (N=26)</th>
<th>BF\textsubscript{10}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.22 ± 15.33</td>
<td>67.42 ± 13.26</td>
<td>0.29\textsuperscript{H0}</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.43 ± 3.5</td>
<td>10.43 ± 3.46</td>
<td>0.12\textsuperscript{H0}</td>
</tr>
<tr>
<td>Interval (days)</td>
<td>32.17 ± 43.35</td>
<td>28.62 ± 41.52</td>
<td>0.59</td>
</tr>
<tr>
<td>Lesion Size (n. voxels)</td>
<td>166833.57 ± 115216.26</td>
<td>117802.18 ± 122448.57</td>
<td>0.01\textsuperscript{H0}</td>
</tr>
<tr>
<td>DSO (range 0-6)</td>
<td>4.49 ± 0.73</td>
<td>0.0 ± 0.0</td>
<td>&gt; 150\textsuperscript{H1}</td>
</tr>
<tr>
<td>MRC-UUL</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>Scores are equal \textsuperscript{H0}</td>
</tr>
<tr>
<td>Proprioception (max = 9)</td>
<td>4.96 ± 2.79</td>
<td>4.65 ± 3.01</td>
<td>0.02\textsuperscript{H0}</td>
</tr>
<tr>
<td>Bisiach scale (max =3)</td>
<td>1.63 ± 1.14</td>
<td>1.67 ± 1.25</td>
<td>0.03\textsuperscript{H0}</td>
</tr>
<tr>
<td>Comb (right bias, cut-off = -0.11)</td>
<td>-0.39 ± 0.32</td>
<td>-0.23 ± 0.41</td>
<td>0.02\textsuperscript{H0}</td>
</tr>
<tr>
<td>Line cancellation (max = 36)</td>
<td>19.91 ± 11.26</td>
<td>21.19 ± 13.24</td>
<td>0.27\textsuperscript{H0}</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>3 ± 1.54</td>
<td>3.46 ± 1.7</td>
<td>0.06\textsuperscript{H0}</td>
</tr>
</tbody>
</table>

**Results**
Results from the clinical and neuropsychological assessment, with comparison between the two groups, are shown in Table 1. The two groups differed only in their level of DSO, as expected.

In a first step of analysis, we examined the grey and white matter structures involved in DSO, using two separate linear regressions, and controlling for extraneous demographic, clinical and neuropsychological variables (see Methods - Statistical Analyses). We found that DSO was associated with right-hemisphere grey matter damage to the Pars Opercularis of the Inferior Frontal gyrus (IFG; BA 6, 45; p = 0.003), the Pre-central gyrus (PrCG; BA 4; p = 0.003), the Post-central gyrus (PsCG; BA 4; p = 0.003), and the Supramarginal gyrus (SMG; BA 40; p = 0.003) (Fig. 1a). Additionally, damage to several white matter tracts were associated with DSO, comprising the Frontal Inferior Longitudinal Fasciculus (FIL; p = 0.008), the Fronto-Insular tract 5 (FIT5; p = 0.008), the Anterior Segment (AS) of the Arcuate Fasciculus (p = 0.009), the second (p = 0.009) and third (p = 0.008) branches of the Superior Longitudinal Fasciculus (SLFII; SLFIII), and the Corpus Callosum (CC; p = 0.009) (Figs. 1 & 2a-c).

In a second step of analysis, we aimed to identify which of these structures account for DSO symptoms, over and above explaining concurrently observed clinical and neuropsychological deficits. To do this, Bayesian Bernoulli Models (BBMs) of each cortical area and white matter tract were compared with a null model containing only the clinical variables (see methods for details). All structures except the CC (BF10 = 0.795) and Pars Opercularis (BF10 = 2.692), provided a better explanation for DSO symptoms rather than simply accounting for the concurrent clinical variables (BFs10 > 3, minimum BF10 = 7.044; Fig. 2d). These two lesion sites were not, therefore, considered in the next step of our analyses, in which we aimed to identify the network of structures that form the neuroanatomical basis of core DSO symptoms.

Silhouette analysis (37 see methods) was used to identify two clusters as the optimal number of clusters needed to explain DSO symptoms. K-means clustering (38 see methods) then identified the components of these two clusters, both of which contained the same anatomical areas, as detailed in Fig. 2e. A Bayesian Gaussian Model subsequently showed that the two clusters explained equally well the observed severity of DSO symptoms (BF10 = 0.3; Fig. 2e, left/grey-shaded panel). Thus, as a final step we used Bayesian Gaussian Models to assess the level of agreement between the two clusters in terms of proportion of damage in each grey matter lesion and probability of each of the white matter disconnections. Results of this analysis indicated that FIT5 (BF10 = 0.0519), FIL (BF10 = 0.198) and SMG (BF10 = 0.253) had equal contributions across the clusters (Fig. 2e). By contrast, results for SLFIII and AS were not conclusive (BF10 = 0.459 and 1.099, respectively), and there are differences between the two clusters in the involvement of SLFII (BF10 = 20.140), of PsCG (BF10 = 3.420) and of PrCG (BF10 = 5.622) (Fig. 2e).

Discussion

The sense of body ownership (SBO) has most recently been understood less as a fixed mental representation of the body in the brain, and more as a dynamic process of multisensory integration6–8, subject to both top-down factors and bottom-up sensory signals11,12. According to one view, the
convergence of these top-down and bottom-up processes amounts to probabilistic inferences about the most likely cause of one's sensory experiences given prior learning and the salience of sensory signals in given multisensory, spatial and social contexts. It follows that the SBO would rely not only on cortical areas associated with sensory processing and multisensory integration in the premotor and parietal cortex, but also on wider brain networks responsible for salience monitoring and belief updating, and supported by fronto-parietal and fronto-insular connections. To provide causal evidence for this hypothesis we used advanced lesion mapping analyses and examined the brain disconnections associated with disturbed sensation of body ownership (DSO) in a large sample of patients with damage to the right-hemisphere. Furthermore, to go beyond the limitations of previous neuroanatomical studies of DSO that have not been able to account for either the confounds of concomitant symptoms, or the combined role of observed lesions and white matter disconnections at the network level, we applied cluster analyses on the resultant lesion patterns to identify the network of structures associated with DSO symptoms and not with other neuropsychological symptoms.

Our results revealed a major role of white matter disconnections in DSO that, when combined with direct grey matter lesions to the parietal cortex (mainly Supramarginal gyrus, SMG), revealed that DSO is the result of disruption to a fronto-insular-parietal-network. Specifically, we found strong evidence for the involvement of disconnections of the fronto-insular (FIT5) and the Frontal Inferior Longitudinal (FIL) tracts to this network. We also found evidence that damage to central gyrus areas and disconnections of the SLFII is of smaller, additional contribution to DSO, while the degree of involvement of the anterior segment of the Arcuate Fasciculus (AS) and the third branch of the superior longitudinal fasciculus (SLFIII) remains inconclusive. Correspondingly, we conclude that the SBO requires the convergence (i.e., integration) of a number of cognitive processes, rather than being purely the functional role of a segregated cortical area. Indeed, this interpretation is consistent with the dynamic features of DSO, revealed by experimental manipulations that allow patients to temporarily recognise their own arms, or dummy arms as belonging to the self, including experimental studies that manipulated the salience and emotional value of sensory stimulations. Our findings indeed revealed that frontal and insular disconnections play a crucial role in the emergence of DSO. The role of the insula in the sense of body ownership is well known, interpreted either as contributing to the integration of interoceptive sensations with other signals about the body, or as regulating the salience of sensory signals, including during belief updating about sensory states and self-awareness. Indeed, the insula is also part of the salient network, a large-scale brain network identified in resting state fMRI studies and connectivity analyses and thought also to relate to the ventral attention network (VAN), involving the temporoparietal junction and the ventral frontal cortex, connected by the ventral branch of the SLF. While damage to this later track was found to be part of the core disconnections of another right hemisphere disruption of the bodily self, namely motor unawareness, or anosognosia for hemiplegia, the present study produced inconclusive results regarding the degree of its involvement in DSO. Instead, we found stronger evidence that DSO is predicted by damage to the FIT5, which links the sub-central gyrus to the anterior long gyrus of the insula and the
FIL that connects the PrCG to the ventral part of the middle frontal gyrus and the superior part of the inferior frontal gyrus, reaching anteriorly the frontal pole\textsuperscript{44}.

The SMG, in the inferior parietal lobe, and to a lesser degree the precentral and postcentral gyrus, were the only grey matter areas involved in DSO symptoms when the contribution of the anatomical structures was compared with that of the remaining clinical variables (null model). The SMG is implicated in multisensory integration and particularly the spatial coding of incoming sensations\textsuperscript{39,45} and actions\textsuperscript{46}. In addition, the SMG is involved in implicit mentalising\textsuperscript{47} and the self-other distinction, and particularly the inhibition of emotional egocentricity\textsuperscript{48} as also demonstrated by the experimental induction of out-of-body experiences (e.g.\textsuperscript{49}). However, although necessary, SMG damage does not appear sufficient to explain DSO symptoms in isolation, and the involvement of the precentral and postcentral gyrus appears even weaker.

The main limitation of the study is related to manual lesion delineation and registration methods and the sensitivity level of neuroimaging techniques that do not depict the full extent of damage produced by stroke lesions\textsuperscript{50}. However, these limitations mainly apply to small sample studies, while here the relatively large number of patients investigated and the strict criteria of inclusion in the two groups (that excluded the doubt diagnoses) reduce these risks.

In conclusion, on the basis of an advanced grey and white matter symptom-lesion and disconnection mapping study, we demonstrate a core fronto-insular-parietal network for the sense of body ownership (SBO). We suggest that the SBO is not limited to bottom-up processes of multisensory integration, but it involves the convergence between such processes, and top-down control and monitoring of sensory salience in different contexts.

**Materials And Methods**

**Patients**

To explore the neural correlates of the sense of body (dis)ownership, a consecutive sample of 135 right hemisphere stroke patients, with dense left-sided hemiplegia, were screened at two stroke units located in Italy (Rehabilitation Department, IRCSS Sacro Cuore Hospital in Negrar, Verona, Italy) and the United Kingdom (Acute Stroke Rehabilitation Unit, St. Thomas Hospital, London). These patients included 132 who had previously taken part in two studies on anosognosia for hemiplegia\textsuperscript{32,51}. Seventy-five patients met the inclusion criteria: (i) unilateral right hemisphere damage, secondary to a first-ever stroke, as confirmed by clinical neuroimaging (MRI or CT); (ii) severe plegia of contralesional upper limb (Medical Research Council - MRC scale = 0;\textsuperscript{52}). Exclusion criteria were: (i) previous history of neurological or psychiatric illness; (ii) medication with severe cognitive or mood side-effects; (iii) severe language, general cognitive impairment, or mood disturbance that precluded completion of the assessment. Structural neuroimaging and clinical data were collected from the included patients, who were subsequently divided into two groups according to the presence/absence of DSO. DSO group
classification (presence/DSO + vs. absence/DSO-) was established according to an interview adapted from previous studies\textsuperscript{13,24,27}. Three questions were asked with reference to the patient's left hand (moved to the ipsilesional field to reduce neglect): i) “Is this your hand?”; ii) “Do you ever feel as if this was not your hand?”; iii) “Does it belong to someone else?”. Patients' responses to each question were scored by two expert clinicians, with 0 = patient recognizes the arm as belonging to him/her; 1 = uncertain answers indicating doubts about ownership; 2 = responses indicating disownership and/or attribution of the arm to somebody else (min score = 0; max score = 6). Patients scoring ≥ 4 were diagnosed as DSO, while only patients scoring ‘0’ were considered for the control group. This allowed the exclusion of any uncertain cases, where patients did not show clear limb disownership, but gave unclear responses, for example due to somatosensory disorders or affective components (e.g., “I would like the arm was not mine”; “I don't feel like it is mine as I don't experience any physical sensations from it”).

The resulting sample (N = 49) comprised 23 DSO + patients and 26 DSO- controls. All patients gave written, informed consent and the research was conducted in accordance with the guidelines of the Declaration of Helsinki (2013) and approved by the Local Ethical Committees of each location.

**Neurological and neuropsychological assessment**

There were no differences in age and education between the two groups. As the data were collected from different units, only the scores in the neuropsychological tests that were administrated in both the centers were considered (Table 1).

Proprioception was assessed by asking the patients to state whether or not they felt a passive movement administered to an upper limb joint (i.e. index finger, wrist, and elbow\textsuperscript{53}). Personal neglect was assessed by means of the ‘Comb’ subtest, of the ‘Comb and Razor test’\textsuperscript{54}, while patients’ score on the Line cancellation subtest of the Behavioral Inattention Test (BIT) was considered as a measure of extrapersonal neglect\textsuperscript{55}. The backward digit span scores\textsuperscript{56} served as index of working memory. Anosognosia for hemiplegia (AHP) was assessed via the Bisiach’s scale\textsuperscript{57,58} for scoring.

**Lesions drawing and disconnection maps**

Neuroimaging data were acquired via Computerized Tomography and Magnetic Resonance (CT = 89%; MRI = 11%) and lesions were segmented and co-registered using an established manual procedure\textsuperscript{13,27,32}. The lesion drawing was independently performed by two experts, who were blind to the patients’ group classification. In cases of disagreement on the extension or the site of a lesion, a third anatomist’s opinion was consulted.

Scans were registered on the ICBM152 template of the Montreal Neurological Institute, furnished with the MRcron software (ch2, http://www.mccauslandcenter.sc.edu/micro/mricron/). First, the standard template was rotated on the three plans (size: 181 x 217 x 181 mm, voxel resolution: 1 mm\textsuperscript{2}) to match the orientation of the patient’s MRI or CT scan. Lesions were outlined on the axial slices of the rotated template. The resulting lesion volumes were then rotated back into the canonical orientation, to align the
lesion volumes of each patient to the same stereotaxic space. Finally, to remove voxels of lesions outside the white and grey matter brain tissue, lesion volumes were filtered by means of custom masks based on the ICBM152 template.

Disconnectome maps were computed with the ‘disconnectome map’ tool of the BCBToolkit software\textsuperscript{34}. The first step of the procedure is the tracking of white matter fibres passing through each patient’s lesion, by means of the registration of lesions on the diffusion-weighted imaging dataset of 10 healthy controls\textsuperscript{59}. This produces a percentage overlap map that takes into account the inter-individual variability of tractography in a healthy controls’ dataset. Therefore, in the resulting disconnectome maps computed for each lesion, voxels show the probability of disconnection (from 0 to 100\textsuperscript{60}). These disconnection probabilities of each patient were used as a predictor variable in subsequent analyses (see Statistical analyses section).

**Statistical analyses**

**Clinical and neuropsychological variables**

A comparison of the clinical and neuropsychological variables between the two groups was executed by means of Bayesian linear models. Unlike traditional frequentist statistics which only allow inferences to be made on the basis of rejecting the null hypothesis, these Bayesian models allow both the null (i.e. no differences between groups) and alternative (i.e. differences between groups) hypotheses to be accepted or rejected (see\textsuperscript{61}). Bayes Factors (BF\textsubscript{10}) were calculated, with BF\textsubscript{10} > 3 indicating that the alternative hypothesis should be accepted, a BF\textsubscript{10} < 1/3 indicating that the null hypothesis should be accepted, and results within 3 and 1/3 being inconclusive. In this latter case, it is considered as valid to accept the null (simpler) model (for the principle of the Ockham’s razor; see\textsuperscript{62}). To compare results that are expressed in different scoring ranges, all the scores from neuropsychological tests were transformed to z-scores, with higher scores corresponding to better performances. Missing data (11\% of the total clinical and neuropsychological data) were replaced by means of multivariate imputation by chained equations using the \textit{mice} package\textsuperscript{63} in R ver. 4.0.0\textsuperscript{64}.

**Sites of lesion and tract disconnections.**

Two separate linear regression analyses were used to explore differences in lesion sites and tract disconnections between the two groups, both using the same procedure via the tool “randomize” (89.Winkler et al., 2014), part of FSL package (http://www.fmrib.ox.ac.uk/fsl/, version 5.0), which performs nonparametric statistics on neuroimaging data. Data on lesion size, lesion onset-neuroimaging interval\textsuperscript{65}, anosognosia, personal and extrapersonal neglect, working memory, and proprioception were used as covariates. Threshold-Free Clusters Enhancement option was applied to boost cluster-like structures of voxels, and results that survived the 5000 permutations testing were controlled for family-wise error rate (p > 0.95).
To identify the grey matter structures emerging as significant from the regression analysis, results were compared with the probability maps of the correspondent anatomical structures (thresholded at 60%) in the Harvard-Oxford Atlas\textsuperscript{66}. This allowed us to compute the proportion of grey matter structures affected by each patient's lesion. Similarly, to identify the disconnected white matter tracts on the disconnection results, the tracts probability maps (thresholded at 80%) of an atlas of human brain connections\textsuperscript{43} were used. The masks were also used to extract the probabilities of disconnection for each tract from each patient's disconnectome map.

**Contribution of grey and white matter structures in DSO**

With the purpose of understanding if, in addition to the clinical variables, each single lesion site (grey matter) or tract disconnection was able to explain the DSO symptomatology better than the clinical variables alone, Bayesian Bernoulli models were used. For each structure and tract separately, a null model was fitted with DSO symptoms (1 = present, 0 = absent) regressed on the clinical variables scaled on a [-1, 1] range (lesion size, lesion-onset/neuroimaging interval, anosognosia, visuo-spatial neglect – Line Cancelation test –, personal neglect – Comb test –, working memory – Digit Span Backward – and proprioception scores). The null model was compared with other models where the DSO symptoms were regressed on the probability of disconnection of the white matter tract or on the proportion of the lesioned grey matter structure ([0, 1] range) plus the clinical variables (alternative hypothesis models). When the Bayes Factor was in favour of the alternative hypothesis model (i.e., the structure considered + the clinical variables explained the DSO symptoms better than the clinical variables alone), that white or grey matter structures were used in the following step.

Here, the possibility that the damaged structures found to occur in DSO are organized in neural networks was investigated. For this, the optimal number of clusters was calculated by employing the Average Silhouette method on DSO patients\textsuperscript{37}. Then, the clusters were determined via the K-means algorithm\textsuperscript{38}. After this, to identify which (if any) cluster explains DSO symptoms better, a Bayesian Gaussian Model was fitted, with the raw DSO severity score as dependent variable (range: \{4, 5, 6\}) and the division in clusters and the clinical variables as regressors (scaled in the [-1, 1] range). This model was compared to a null model with the same dependent variable and the scaled clinical variables as regressors.

Finally, the proportion (grey matter) or the probability (white matter) of each damaged structure was compared between the two clusters (controlling for the scaled clinical variables) by means of Bayesian Gaussian Models (again, each alternative model – i.e. cluster and control clinical variables was compared to the null model - control clinical variables alone). The goal of this analysis was to understand which structures were damaged in an equivalent degree in both clusters.

Cluster and Bayesian analyses were computed in R ver. 4.0.0\textsuperscript{64}. Bayesian models were fitted by means of the \textit{brms} package\textsuperscript{67}, with 4 chains of 100,000 iterations each one and 10,000 burn-in steps, for a total of 360,000 samplings. Comparisons between Bayesian models were carried out using BF\textsubscript{10}\textsuperscript{68}. BF\textsubscript{10} were computed by using the \textit{bridgesampling} package\textsuperscript{69}. Bayesian Bernoulli models had Cauchy distributions
with mean 0 and scale 10 as priors for the regressors, and the Bayesian Gaussian models used Cauchy
distribution, with mean 0 and scale 10 for the regressors, and mean 0 and scale 1 for the intercept, as
prior distributions. For the average silhouette method, the Factoextra package\textsuperscript{70} was used.

### Declarations

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#### Author Contributions

Valentina Moro, Conceptualization, Project administration, Data curation, Investigation, Methodology,
Writing-original draft, writing-review and editing; Valentina Pacella, Data curation, Formal Analysis,
writing- original draft, writing review and editing; Michele Scandola, Conceptualization, Formal Analysis,
Methodology, writing review and editing; Sahba Besharati and Elena Rossato, Investigation, writing review
and editing, Paul Jenkinson and Akaterini Fotoupoulou, Conceptualization, Supervision, Validation,
Methodology, Writing original draft, Writing-review and editing.

#### Competing interests

The author declares no competing interests.

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Figures

Figure 1

a) Statistical mapping of the lesions resulting from the comparison between DSO and control groups. PsCG: postcentral gyrus; PrCG: precentral gyrus; Pars Oper: pars opercularis of the inferior frontal gyrus; SMG: supramarginal gyrus. b) Statistical mapping of the brain disconnections in DSO when compared with the control group. FIT5: fronto-insular, tract 5. SLFIII: third branch of the superior longitudinal fasciculus. AS: anterior segment of the arcuate fasciculus; SLFII: second branch of the superior
longitudinal fasciculus. FIL: frontal inferior longitudinal tract of the frontal longitudinal system. CC: corpus callosum. Colour bar represents the p-value statistic, only significant voxels are shown (p < .05).

Figure 2

a) Lateral and b) medial view of the reconstruction of the white matter tracts contributing to DSO (BF10>3). AS = anterior segment of the arcuate fasciculus. SLFIII = third branch of the superior longitudinal fasciculus. SLFII = second branch of the superior longitudinal fasciculus. FIL = frontal inferior longitudinal tract. FIT5 = fronto-insular tract 5. c) Identification on a brain template of the grey matter structure contributing to DSO (BF10>3). PrCG = precentral gyrus. PsCG = postcentral gyrus. SMG = supramarginal gyrus. d) Bayes Factor for each anatomical result’s model representing the hypothesis that the damage to grey matter structure/tract disconnection contributes to the emergence of DSO, against the
null model. e) Posterior Distributions (PD) from the Bayesian Analysis of DSO patients’ grouping along the 2 clusters obtained from the Silhouette analysis. The violin plots represent the PDs obtained from the Bayesian Analysis; the upper and lower boundaries of the box are the boundaries of the 95% Highest Density Interval of the PD; the midline is the Mode of the PD. The first variable on the x-axis (grey-shaded background) represents the DSO mean severity score for each cluster (range 0 - 6, left-side y-axis). On the right part of the plot, the proportions of grey matter structures and the disconnection probability of the tracts involved in each cluster are represented (range 0 - 1, right-side y-axis). = stands for BF10 < 1/3; ≠ stands for BF10 > 3.