The analysis of semantic networks in multiple sclerosis identifies preferential damage of long-range connectivity

Elena Abada, Jorge Sepulcre, Elena H. Martinez-Lapiscina, Irati Zubizarreta, Jordi Garcia-Ojalvo, Pablo Villoslada

1. Introduction

Brain networks are damaged in neurological diseases, disturbing cognitive performance such as semantic memory (Sepulcre et al., 2012, 2009, 2008). Verbal fluency tests are used routinely to quantify global semantic memory output, and extracting semantic networks from these tests might provide additional information about the way the human brain stores and retrieves information when cognition is impaired (Lau et al., 2008; Steyvers and Tenenbaum, 2005). We previously developed a model of human semantic networks based on statistical co-occurrence in verbal fluency tasks using graph theory (Goni et al., 2011). In that model, the degree of co-occurrence between consecutive words (up to second neighbors) was measured in data from categorical fluency tests and when co-occurrence surpassed a given threshold, the two words (network nodes) were considered to be associated by a link (network edge). Using 200 fluency tests in the animal category from healthy individuals we obtained the semantic networks, which showed high modularity, displayed small-world architecture (Villoslada et al., 2009), and nicely reproduced classical definitions and measures of clustering and switching transitions (Troyer et al., 1997).

Previous analysis of verbal fluency tests in MS patients showed only a slight decrease in the total number of words, yet a consistent decrease in the switching score between subcategories was observed, as well as an increase in cluster size (Sepulcre et al., 2011; Joly et al., 2014). These observations suggest that a failure occurs in the retrieval of lexical information rather than a consistent reduction of the lexical pool. In addition to counting the number of words or their semantic similarity, one can also develop a representation of the connections between words using a statistical threshold (Goni et al., 2011), which counts how often words appear consecutively or close along the fluency tasks, representing semantic relations between words. This encouraged us to apply network analysis to semantic networks arising from this model in
order to explore the mechanisms underlying the alterations in semantic memory associated with MS.

Network analysis provides a tool for analyzing complex datasets with quantitative measurements that can be applied to the case of semantic output. In graph theory, a network is represented by a set of elements (vertices or nodes) that are connected in terms of specific relationships (links or edges). Studying the network properties allows for the identification of highly connected elements (so-called hubs), hierarchical organizations or critical nodes in the network cohesion. In addition, quantifying its size by counting the number of nodes and edges helps to further characterize the network (Barabasi et al., 2011). In order to analyze semantic networks, three different levels of analysis can be used: (i) the word level, focusing on specific nodes in the network, such as the most connected nodes (the largest nodes or hubs) and nodes of centrality that are related to the vulnerability of the network (cohesive nodes); (ii) the word group level, examining highly connected groups of nodes (neighborhoods in the network); and (iii) the word network level, corresponding to topological properties of the network as a whole (e.g. small-world phenomenon (Watts and Strogatz, 1998)). Moreover, as opposed to the classical definitions of lexical access strategies considered in verbal fluency tasks, we analyzed concepts like clustering and switching from the semantic network perspective.

The aim of this study was, using data from verbal fluency tests, to assess the semantic networks of MS patients and compare them with those of controls. The network structures formed from the statistical co-occurrence of concepts in the tests contain, albeit indirectly, information on the amount of content that is accessed during the test (number of words/nodes) as well as the routes or paths that are followed during content retrieval in the memory task of the fluency tests (links/edges).

2. Methods

2.1. Subjects

Patients with MS were recruited by their neurologist, providing their signed informed consent. Patients with MS were diagnosed according to the McDonald 2005 criteria (Polman et al., 2005). Demographic and clinical features of the cohorts are described in Table 1. Patients in an active phase of MS relapse, taking steroids, according to the McDonald 2005 criteria (Polman et al., 2005). The Institutional Review Board at our center approved this study.

Table 1

Demographics and clinical data of MS patients and controls. The data are expressed as the mean ± standard deviation, or the median and range or proportions, depending on the parametric or non-parametric distribution of the variable. The p-value is the mean of the Mann-Whitney U-test.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=200)</th>
<th>MS (n=36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex female n [%]</td>
<td>117 [58%]</td>
<td>27 [75%]</td>
<td>ns</td>
</tr>
<tr>
<td>Age (year)²</td>
<td>32 ± 12</td>
<td>36 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>Education (year)²</td>
<td>15 (5–30)</td>
<td>15 (7–28)</td>
<td>ns</td>
</tr>
<tr>
<td>Verbal fluency test¹</td>
<td>30 ± 6</td>
<td>25 ± 5</td>
<td>0.00004</td>
</tr>
<tr>
<td>EDSS</td>
<td>–</td>
<td>2.5 (0–7)</td>
<td>–</td>
</tr>
<tr>
<td>DMD (Y/N)</td>
<td>–</td>
<td>15/21</td>
<td>–</td>
</tr>
</tbody>
</table>

ns, No statistically significant differences between groups; –, not applicable.

EDSS: Expanded disability status Scale; DMD: Disease modifying drug.

¹ Mean ± standard deviation.
² Median or means, range in parentheses.

Patients were assessed for cognitive impairment with the BRB-N test as previously described (Sepulcre et al., 2006), and patients with severe cognitive impairment (defined as > 3SD in 3 subtests, which represents 30% of patients with MS (Sepulcre et al., 2006)) were excluded from the study. We did not assess levels of fatigue, a factor known to influence cognitive performance (Weinges-Evers et al., 2010; Andreasen et al., 2010; Flachenecker and Meissner, 2008), but tests were performed in the morning, when patients typically experience less fatigue. All patients had an MRI study in the previous 3 months before testing, including T1, T2 Flair and T1 post-gadolinium. Although MRI scans were not used to exclude patients due to the relationship between inflammatory activity and cognition (Bellmann-Strobl et al., 2009), no participants were experiencing significant disease activity at the time of the study as measured by new gadolinium enhancing lesions. Finally, only right-handed (＞70% Oldfield scale (Oldfield, 1971)) native Spanish-speakers took part in the study. We also analyzed a cohort of sex, age and education matched control subjects. The Institutional Review Board at our center approved this study.

2.2. Verbal fluency tests

MS patients and controls were asked to name as many animals as possible in 90 s. All tests were performed by the same neuropsychologist and at the same time of the day (between 9 am and 1 pm). In these verbal fluency tests, proper names were not allowed and all the responses were transcribed verbatim. Repetitions and rule violations were not included when calculating the total verbal fluency scores. None of the individuals had previously been subjected to this test and none refused to perform it. Also, this test is less sensitive to longitudinal changes than other cognitive domains (Duque et al., 2008). No subjects suffered clinical reactivation of the disease during the neuropsychological assessment at baseline or at the endpoint of the study.

2.3. Building semantic networks and resampling methods

Semantic networks were built using a method based on co-occurrence statistics, as described previously (Goni et al., 2011). To address the difference in dataset sizes between the patient and control groups (number of individual tests), we performed statistical resampling using a jacknifing method (tests resampling). We initially dealt with the difference in size of each dataset: 36 tests from MS patients and 200 tests from controls. From the control dataset we evaluated the different combinations of 36 tests without repetitions, improving the final statistical power. Second, for each combination of 36 control and disease tests we computed distinct subsamples of 25 tests (without repetitions) through random permutations (at least 800 replicates). We built semantic networks by using a co-occurrence statistical model to link words (by edges in the graph) and we extracted the giant network component matrix (the maximum connected component) for each subsample of tests. Finally, we computed the different topological
properties of the networks in order to perform statistical analyzes on all the replicates in both the disease and control states. A statistical analysis of the resamples produces non-parametric estimates of the standard error of the measures of interest, and allows hypotheses to be tested and confidence intervals to be calculated. It is important to note that the averages and deviations we computed from our statistical method are not intended to be used to define the semantic networks but rather, they serve for comparative purposes between the disease state and matched controls. The network analysis was performed in Matlab 7.9 (The MathWorks Inc., Natick, MA, USA), topological properties were computed using algorithms from the MIT complex network resources (Non Linear Laboratory, MIT, US) and graphs were drawn using Pajek (http://vlado.fmf.uni-lj.si/pub/networks/pajek).

### 2.4. Statistical analysis of the network’s properties

Comparative topology for the MS patient and control groups, albeit indirectly, may account for possible changes in the underlying brain memory processes, such as in the co-occurrence of concepts during fluency verbal tests, since it is known that network design is typically crucial for function. The topological properties we analyzed included: the number of nodes and edges (number of words and links between words); the average connectivity degree (average number of links per node); the average clustering coefficient (the connectivity between different neighbors of a given node); the assortativity coefficient (the connectivity between nodes of equal connectivity degree); the maximum node-betweenness centrality (score which measures the most critical node in maintaining the maximum cohesion, or in other words, measures a type of vulnerability in the network); and the cyclomatic number (which counts the minimum number of cycles – cycles being the sequences of links starting and finishing at the same node), a score we associate with available routes for concept retrieval in the network (Barabasi and Oltvai, 2004). To help visualize the network properties we include some schemes in the Supplementary material (Fig. S1).

These properties were computed in each of the network subsamples built by the jackknife approach and the value distributions were then plotted by density estimates using kernel-smoothing functions with an optimal bandwidth. For the control group, we plotted the average of the density distributions from different trials of 36 tests among a total of 200 tests, and included the associated standard deviations in Fig. 2. We compared control and MS values for each property using the two-sample Kolmogorov–Smirnov test (non-parametric test) to evaluate statistical differences between both groups. Averages and deviation values for each property can be found in Table 2.

### 2.5. Analysis of clustering and switching transitions in semantic networks

Switching and clustering transitions are two lexical access strategies frequently assessed in verbal fluency tasks (Troyer et al., 1997, 1998), including those associated with MS (Sepulcre et al., 2011), in clinical practice. Clustering refers to the generation of consecutive words or concepts with semantic or phonemic relationships (subcategories) and switching refers to shifting between subcategories. In semantic fluency it is common to count words that belong to the same semantic subcategory (e.g., in animal category tests like pets, birds, farm animals, insects, etc.), defining clusters of related words. In our network study we wanted to include a statistical evaluation that was analogous to these two types of transitions between consecutive words, re-defining clustering or switching according to whether or not the concepts (animal names) are directly linked in the reference network from control individuals (Goni et al., 2011).

### 3. Results

Semantic networks were generated in which the edges or links represent significant co-occurrence between words (nodes) in the tests (Fig. 1). Functional efficiency in semantic networks is based on the premise that more nodes in the network means more stored data (semantic memory), although the connections between these nodes (i.e.: the topological characteristics of the network) provide markers of the efficiency of information retrieval. The graphs revealed a clear organization into neighborhoods or modules, with semantically related nodes appearing in all groups and with major classes, such as jungle animals (elephant, lion, tiger, giraffe...), insects (fly, ant, bee, mosquito...), marine animals (salmon, dolphin, whale...), farm animals (chicken, pig, horse, sheep...) or pets (cat, dog...), as previously described for control individuals (Goni et al., 2011). The content of the semantic networks from MS patients was noticeably inferior to that of the matched control networks, both in terms of nodes and edges (Fig. 1a and b). However, the network complexity and cluster hierarchy of related words seemed to be preserved.

In order to compare the topological properties of the semantic networks in MS, we plotted the probability density functions of common network descriptors (number of nodes, edges, average degree, clustering coefficient, assortativity and centrality) obtained from network subsamples as described in Section 2. Semantic networks from MS patients were smaller, with fewer nodes and edges scattered in a narrower distribution than that of the controls (red and black circles, respectively in Fig. 2a and b). As expected from previous studies of verbal fluency in the animal category, MS patients produced fewer words on average than matched controls (31 ± 7 vs 27 ± 5; p < 0.05). Likewise, in the network analysis the number of nodes (words) found in the MS patient network was on average smaller than that in the network of matched controls (20 ± 6 vs 37 ± 2, respectively, p < 0.01; Table 2). This reduction is also reflected in the number of connections per node, which means that the average degree in MS decreases and distribution is shifted towards lower values (Fig. 2c). However, the loss of degree does not seem to be consistent with changes in the number of links between neighbors. The local connectivity, as measured by the average clustering coefficient, was similarly distributed in a wide range for both MS and the control networks and shifted

### Table 2

Statistics of the topological features of the control and MS semantic networks. Statistics from control and MS networks are shown for the different topological features from tests resampling performed in MS and control. Significant differences between disease and control were assessed by Mann–Whitney U-test (non-parametric). The data are expressed as the mean ± standard deviation, median in parentheses.

<table>
<thead>
<tr>
<th>Network descriptors</th>
<th>Controls</th>
<th>MS patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes</td>
<td>37 ± 2 (34)</td>
<td>20 ± 6 (19)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Edges</td>
<td>47.0 ± 2.5 (43)</td>
<td>23 ± 8 (22)</td>
<td>0.002</td>
</tr>
<tr>
<td>Degree (average)</td>
<td>2.51 ± 0.02 (2.5)</td>
<td>2.3 ± 0.2 (2.3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Clustering coefficient</td>
<td>0.23 ± 0.01 (0.23)</td>
<td>0.27 ± 0.11 (0.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Assortativity</td>
<td>−0.07 ± 0.03 (0)</td>
<td>−0.26 ± 0.16 (−0.25)</td>
<td>0.003</td>
</tr>
<tr>
<td>Betweenness</td>
<td>0.92 ± 0.04 (0.92)</td>
<td>1.0 ± 0.1 (1.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cyclomatic number (num. cycles; normalized)</td>
<td>0.29 ± 0.02 (0.28)</td>
<td>0.24 ± 0.09 (0.23)</td>
<td>3E–6</td>
</tr>
<tr>
<td>Triangles (num. cycles; normalized)</td>
<td>0.26 ± 0.02 (0.28)</td>
<td>0.22 ± 0.09 (0.21)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Goni et al., 2011.
towards higher values (Fig. 2d). These results suggest that the network representing memory tasks from MS patients exhibits fewer concepts (nodes) as well as fewer associative relationships between them (links), although the local network architecture does not seem to be highly modified, therefore the ability to associate animals in the same sub-category is preserved.
With regard to the cohesiveness of these networks, we found an obvious difference in MS compared to controls. MS graphs contain a larger number of 'central' nodes, that is, nodes supporting single tracks of connection (Fig. 1a and b). The maximal node-betweenness scores were higher in the MS group (Fig. 2f). In other words, we found more nodes supporting a central weight in cohesion structure and therefore, positions of vulnerability in the MS network in cases of node failures, since there are no alternative routes for communications between distant nodes (alternate routes).

Another distinguishable feature between the two topologies compared is the correlation between the degrees of connected nodes. Whereas semantic networks from controls are neither assortatives or slightly disassortatives (negative assortativity scores in Fig. 2e), they are ‘disordered’ in terms of connections between nodes, which are uncorrelated to the degree of these nodes (e.g. hubs are not mainly connected to other hubs) and have more negative correlations. MS networks exhibit higher attachment between nodes with different degree than controls (Fig. 2e). From these results, we can only conclude that, in both control and MS, we found ‘disordered’ networks that do not exhibit preferences in their connections beyond clustering similar words.

It is known that in many biological systems at very different levels (from protein networks to brain neural connections), a common network design has been found in which the system elements interact, resulting in a robust and versatile manner, which mean provides an advantage in protecting against damage by some specific attacks. This efficient pattern is the so-called ‘small-world networks’ (Watts and Strogatz, 1998; Barabasi and Oltvai, 2004; Ferrer and Sole, 2001). Considering that co-occurrence semantic networks capture and reflect certain aspects of stored content and how the brain accesses it during memory tasks such as the fluency test, we wondered whether our networks are arranged like these highly efficient ‘small worlds’. Mathematically, small world graphs have average clustering coefficients significantly higher than analogous random networks, and the mean shortest path lengths are comparable. In order to test this, we built random networks according to the model of Erdős–Rényi (Watts and Strogatz, 1998), with a number of nodes and average degree fixed taken from different subsamples in the MS and control groups. The clustering coefficient average for random graphs was $0.08 \pm 0.01$ (mean \pm std), significantly lower than the $0.23 \pm 0.03$ for controls. Similarly, it was $0.12 \pm 0.08$ compared to $0.3 \pm 0.1$ for random MS and MS networks, respectively. The average of shortest path lengths was similar between both groups and their corresponding analog random networks ($3.1 \pm 0.06$ to $5.2 \pm 0.2$; random vs control and $2.6 \pm 0.4$ and $3.8 \pm 0.8$; random vs MS). These results indicate that both MS and control topologies support the main characteristics of small-world networks, such as high clustering levels and short average path lengths.

Furthermore, the small-world graphs are characterized by the presence of bridge nodes that are not necessarily hubs or critical connectors in the cohesion of the network but rather, are bridges between distant nodes giving rise to new pathways that enhance the storage and access to data. We estimated the number of these paths by counting the bridging loops (closed routes) larger than triangles (cycles of three nodes), which are mainly related to clustering (small worlds schemes in Fig. 3). A high number of cycles is related to greater cohesion in the network and more available routes or paths to retrieve stored data (in undirected and

![Fig. 3. Small-world architecture and bridge nodes in semantic networks.](image-url)
unweighted networks such as our semantic networks). Then, the cyclomatic number allowed us to quantify and compare the number of cycles normalized to the network size (number of nodes), showing that the MS network had a lower cyclomatic number than the control network (MS, 0.24 ± 0.09; controls, 0.29 ± 0.02). In fact, most loops in MS networks are the smallest ones possible, meaning ‘triangles’ (closed path of three nodes, Table 2), indicating that the decrease of cycles in MS is mainly due to the loss of cycles larger than triangular connections. Together, these results suggest that semantic networks in MS are not as ‘well-connected’ due to the loss of bridge nodes available for alternative routes leading to what could be defined as a loss of associative capacity, although the clustering of links between neighboring nodes persists.

Despite the overlap in measures such as the connection degree between neighboring nodes (average and clustering degrees) in both groups, we have observed significant differences in the topology of the semantic network in MS compared with controls that could derive from specific neuronal damage in this disease. These network differences suggest increased vulnerability of the semantic memory and thus compromise functionality by loss of access to different words (Iyer et al., 2013; Holme et al., 2002).

Regarding the analysis of clustering and switching transitions in semantic tests, we took 36 individual tests from control and MS data and built a reference control network of 164 tests. We adapted the classical definition for transition types to the network point of view by defining clustering (white squares) and switching (black squares) as being directly linked or not linked in the reference network, respectively (Fig. 4). Both types of transitions were randomly distributed along the tests in controls and MS patients, although clustering mainly predominates at the start of tests. The probability of clustering transitions in MS networks was lower (36% (±10)) than control (41% (±10)), with a relative loss of 12%, as was the average number of spoken words (MS, 25 (±5); controls, 30 (±4)), which was around 16% less in MS networks. In addition to the loss of words already discussed, these data may also suggest that during the memorization task in the fluency tests, MS patients seem to spend less time accessing words by co-occurrence association, thus increasing switching transitions.

4. Discussion

There are many studies showing that brain circuits are usually organized into small-world networks, with dense local connectivity and long-distance connections via bridge-nodes or shortcuts (Stam and van Straaten, 2012), both at the structural and functional levels (Villoslada et al., 2009; Bullmore and Sporns, 2012). Neurological diseases are often associated with brain damage that may differentially affect short-term connections in the gray matter (due to direct damage to neurons or synapses) and long-term connections in the white matter. This damage may be the basis of the phenotype observed and it may also be responsible for changes in the architecture of cognitive networks, such as semantic networks (knowledge representation through relationships between concepts). In the case of MS, a disease that preferentially damages long-tract connectivity (Filippi et al., 2012), we hypothesized that semantic networks would have preserved the global properties of the network architecture, altering only those connectivity properties that are more closely associated with long-range connections. Based on this hypothesis, we analyzed whether such preferential damage to neuronal networks would be translated to the phenotypic level in semantic network architecture (Seeley et al., 2009).

Our network analysis supports this hypothesis, revealing clear signs of poor cohesion of the MS semantic networks, with increasing maximal centrality (network vulnerability (Iyer et al., 2013)). Nevertheless, the MS semantic network maintains a connectivity profile suggestive of a somewhat resilient structure, preserving almost the same average degree and clustering scores between neighbors as the semantic network of controls. In addition, semantic networks from both MS and matched controls follow the two basic small-world properties, which represent an appropriate design for an efficient memory system. Accordingly,
we suggest the importance of ‘bridge-nodes’ in these semantic networks as opposed to those involving direct connections between hubs. However, hubs are ultimately integrators or distributors due to the number of connections and the positioning of their contacts in the network. The loss of such connections could be due to increased centrality without a dramatic decrease in the average degree or clustering of neighboring nodes. Often damage in neurodegenerative diseases is not random, but instead targets specific structures and may involve smaller or larger length scales, from local pathological disorders to structural and functional network-driven vulnerability (Seeley et al., 2009). Anatomical neuronal connectivity in the brain should not be interpreted such as edges in functional or cognitive networks. Cognitive function requires the integration of distributed neural activity in anatomical networks supporting their functional roles (van den Heuvel and Sporns, 2013).

However, semantic and lexical deficits are usually entangled and it is often difficult to distinguish between them using standard fluency tests, in terms of accessing retrieval information during the memory task. In fact, MS patients performed worse on fluency tests (less words in tests). We wondered if the frequency of clustering transitions (consecutive words coinciding with connected pairs of words in semantic network) differed in MS and healthy individuals. Tests from MS patients display a significant 5% decrease in the probability of clustering transitions. We can conclude that there is less co-occurrence of words and therefore, that MS patients have less lexicon retrieval ability in this type of associative memory task as compared to controls.

Regarding the application of this approach to the study of cognitive impairment at the clinical level, we would like to highlight that even though means of semantic network parameters were not highly different between patient and controls, standard deviations were minimal, indicating that the overlap is not very significant. Therefore, the analysis of semantic networks can become a useful test for assessing cognitive impairment in patients with MS. Also, we believe that this method can be used for guiding cognitive rehabilitation. However, new clinical studies are required in order to define which changes in semantic networks are of clinical relevance and their sensitivity for predicting cognitive impairment or recovery.

Our study has some limitations. Fluency tests, in addition to the undoubted lexical–semantic component, are routinely used to measure other cognitive capacities such as executive function since the task involves strategy generation, monitoring of strategy success, and inhibition of previous responses and strategies. Also, it is possible that the semantic networks are largely intact and that the cognitive deficit of MS is actually the speed and strategic use of lexical knowledge, and the integration of lexical systems with prefrontal executive control. For this reason, we cannot exclude the possibility that our results reflect other levels of cognitive impairment outside the semantic domain. Moreover, we did not control for fatigue, which has well-known effects on cognition (Weinges-Evers et al., 2010; Andreasen et al., 2010; Flachenecker and Meissner, 2008). However, patients were evaluated in the morning, when fatigue is usually less severe. While we excluded patients with severe cognitive impairment, we did not control for mild to moderate cognitive impairment in this study. Although sample size was different for patients and controls, differences in the number of tests between both groups did not affect measurements like number of words spoken by controls or patients. This is because the presented numbers are averages of the total number of tests in each group and the two groups had the same runtime to perform the fluency task. Moreover, the statistical process of counting co-occurrence between two words was normalized by the number of words in each test and by the number of tests in each group. The statistical method to build and compare semantic networks (by resampling) in controls and patients was also selected in order to minimize the impact of different sample sizes. However, our analysis also has some advantages compared to other types of analysis. For example, it uses quantitative metrics of the networks built based on statistics of the frequency of occurrences. As such, it does not rely on a subjective definition of what a cluster (e.g. jungle animals) or transition is.

In summary, the study of semantic networks can be used as a tool to measure cognitive impairment in MS, revealing specific patterns that may be useful in clinical practice for categorizing patients with different levels of damage. In order to define the clinical utility of this tool, new prospective studies are required.

Conflict of interest status

Authors declare we have no conflict of interest related with this work.

Role of funding source

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2015.07.002.

References


