Multiscale topological properties of functional brain networks during motor imagery after stroke

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A B S T R A C T
In recent years, network analyses have been used to evaluate brain reorganization following stroke. However, many studies have often focused on single topological scales, leading to an incomplete model of how focal brain lesions affect multiple network properties simultaneously and how changes on smaller scales influence those on larger scales. In an EEG-based experiment on the performance of hand motor imagery (MI) in 20 patients with unilateral stroke, we observed that the anatomic lesion affects the functional brain network on multiple levels. In the beta (13–30 Hz) frequency band, the MI of the affected hand (Ahand) elicited a significantly lower smallworldness and local efficiency (Eloc) versus the unaffected hand (Uhand). Notably, the abnormal reduction in Eloc significantly depended on the increase in interhemispheric connectivity, which was in turn determined primarily by the rise of regional connectivity in the parieto-occipital sites of the affected hemisphere. Further, in contrast to the Uhemi MI, in which significantly high connectivity was observed for the contralateral sensorimotor regions of the unaffected hemisphere, the regions with increased connectivity during the Ahand MI lay in the frontal and parietal regions of the contralaterally affected hemisphere. Finally, the overall sensorimotor function of our patients, as measured by Fugl-Meyer Assessment (FMA) index, was significantly predicted by the connectivity of their affected hemisphere. These results improve our understanding of stroke-induced alterations in functional brain networks.

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I ntroduc t ion

Most brain functions result from the organization of several neuronal assemblies in a complex and dynamic system (Varela et al., 2001). The term “organization” can be defined as the coherent interdependence of various parts that constitute the whole. Functional connectivity (FC) approaches have been introduced to operationally describe the coherent dependence across spatially remote neurophysiological processors (Friston, 1994); such approaches are effective tools for assessing the organization of the brain, based on the activity of multiple cerebral regions.

Over the past decade, graph theory has been introduced as a mathematical approach to characterize the complexity of anatomical and functional brain networks (Bullmore and Sporns, 2009). In functional neuroimaging, a graph is an abstract representation of a pattern of connectivity, in which nodes represent various areas of the brain and links correspond to significant interactions between the activities of regions of the brain. Many groups have exploited graph-based approaches to examine the changes in functional (data-driven) and effective (model-based) connectivity in several brain disorders (He and Evans, 2010). In this regard, many computational studies have focused on understanding how the brain reorganizes its functional structure after stroke from a network-based perspective.

Graph theory approaches have allowed the effect of stroke on the organization of the brain to be studied from neuroimaging signals that are recorded during resting states and motor/cognitive tasks through various noninvasive techniques, such as functional MRI (fMRI) (Nomura et al., 2010; Wang et al., 2010), EEG (De Vico Fallani et al., 2009), MEG (Westlake et al., 2012), and DTI (Crofts et al., 2011). Although the extent to which the application of such approaches impact the study of stroke-related disturbances in cortical connectivity is unknown, they have been reviewed comprehensively, based on recent meta-analyses (Grefkes and Fink, 2011; Westlake and Nagarajan, 2011).

These reviews have highlighted that stroke lesions can lead to i) critical deviation from optimal “small-world” network topologies
that support processing of segregated and integrated information (Bassett and Bullmore, 2006), ii) altered interhemispheric connectivity, and iii) abnormal regional centrality in the ipsilesional and contralesional hemispheres, possibly due to compensatory mechanisms. Although this evidence suggests that stroke modulates several topological attributes of the functional brain network, ranging from small (e.g., single-node connectivity) to large scales (e.g., connectivity of the entire system), a unifying framework that simultaneously describes the changes in network properties on different scales (Alstott et al., 2009) and their relationships (Vázquez et al., 2004) has not been established and is rarely and poorly applied in analyses of functional brain networks.

In this study, we applied a multilevel graph analysis on functional brain networks obtained from EEG signals that was designed to examine multiple topological scales simultaneously. Based on the peculiarity of functional brain networks to be embedded in a physical space that is coincident with the anatomic substrate (Doron et al., 2012), examine multiple topological scales simultaneously. Based on the brain networks obtained from EEG signals that was designed to

### EEG recordings and motor tasks

All patients had EEGs recorded within 1 week after hospitalization. Patients were comfortably seated in a dimly lit room, with their upper limbs resting on a cushion, and instructed by a visual cue to perform a kinesthetic type of MI of their hand grasping (Jeannerod, 1994). In order to ensure the correct understanding of the MI task by the patients, several trials of actual execution of the same sustained grasping with the unaffected hand were performed before the recording session (visual cue and timing as the EEG experimental condition). Afterwards, in the EEG experiment, patients were instructed to rehearse “the feeling of movements” acquired during the previous MI task practice. Similar pre-EEG recording session practice was allowed with the affected hand by attempting grasping movements. The recording session comprised 2 runs in which the MI of the hand grasping relative to the unaffected (Uhand) and affected (Ahand) hand was sustained for 4 s. Each run consisted of 30 trials (8 s each), divided equally between randomly presented baseline and task trials. The visual cue was presented using dedicated software, i.e., BCI2000 (Schalk et al., 2004), that was synchronized with the EEG amplifiers.

As illustrated in Fig. 1, the visual cue was a small red ball that moved at constant speed along the central vertical line of a screen from bottom to top for 8 s (trial duration). In the task trials (panel A), the lower half of the screen was black and the upper half was green. Patients were instructed to be prepared to begin the hand MI as soon as the red ball entered the green area (4 s) and maintain the task until the ball reached the edge of the screen (4 s). In the baseline trials (panel B), the screen was black, and patients simply relaxed throughout the trial duration (8 s).

EEG signals were collected from 61 scalp sites that were assembled on an electrode cap per a montage that was modified as an extension of the international 10–20 system. The electrooculogram (EOG) was simultaneously recorded to allow the subsequent rejection of ocular artifacts. EEG data were continuously acquired on a commercial system (Brainproduct GmbH, Munich, Germany) with a 200 Hz frequency sampling; scalp signals were referenced to the linked-ear signal. The data were then band-pass filtered in the 1–45 Hz range and deconvoluted from ocular artifacts using the Independent Component Analysis tool (ICA) and commercial software (Vision Analyzer software; Brainproduct GmbH, Munich, Germany).

To ensure that the MI task was performed without any concomitant voluntary muscular contraction, the electromyographic (EMG) activity that was recorded in the left and right opponens pollicis was monitored throughout the experimental session using disposable surface electrodes that were placed in a bipolar belly–tendon configuration. The

### Materials and methods

Between 2011 and 2012, we recruited 20 patients (mean age, 55.5 years; 11 females) who were affected by a first-ever unilateral stroke in the subacute phase (time since event, 8.4 ± 2.8 weeks) on admission for poststroke rehabilitation treatment at Fondazione Santa Lucia (Rome). All patients had suffered unilateral supratentorial (cortico/subcortical) stroke (left hemisphere 11) that was confirmed by structural MRI and resulted in various degrees of motor impairment on the side of the body that was contralateral to the stroke lesion (for patient details, see Table 1). Exclusion criteria were: the pharmacological treatment with drugs affecting the patient’s vigilance and/or the EEG background activity; Mini-Mental State Examination score < 24 (Tombaugh, 2005) and severe cognitive disorders (such as severe hemispatial neglect and language disorders) as evaluated by a neuropsychologist; the presence of other chronic disabling pathologies; orthopedic injuries that could impair reaching or grasping; spasticity of the shoulder, elbow, or finger flexors and extensors that exceeded 3 on the modified Ashworth Scale.

The clinical and functional assessment of all patients comprised the following scales: i) the European Stroke Scale (Hansson et al., 1994); ii) the Medical Research Council scale for muscle strength (Compton, 2010) to assess residual strength in the upper limbs; and iii) the upper limb section of the Fugl–Meyer Assessment (Fugl Meyer et al., 1975) to assess functional motor recovery after stroke. Detailed scale scores relative to the clinical and functional assessment are reported in Table 1. All measurements were made by an expert physician less than 1 week before the EEG data acquisition. All patients gave written informed consent for participation in the study, which was approved by the Ethics committee of the Fondazione Santa Lucia.
EMG signals were available to the experimenter to encourage the patients to relax their muscles and avoid movements during the task trials. In the offline analysis, preprocessed EEG signals were segmented considering the last 4 s of each task and baseline trial as the period of interest, as shown in Fig. 1. The segmented traces were then inspected visually to reject any EEG segment that had residual muscular or other pronounced artifacts. Finally, we flipped the functional (EEG time series) and anatomic (scalp electrode positions) data of patients with left-sided lesions along the mid-sagittal plane to perform a group analysis with all 20 patients.

**Functional connectivity estimation**

Brain FC was calculated for the segmented periods of interest (task and baseline) using imaginary coherence (Nolte et al., 2004), which is a robust estimate of synchronization between 2 time series in the

**Table 1.** Demographic, clinical, and functional characteristics of the stroke patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Hand</th>
<th>Lesion side</th>
<th>Lesion type</th>
<th>MRC</th>
<th>FMA</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>43</td>
<td>F</td>
<td>12</td>
<td>L</td>
<td>Left fronto-parietal, basal ganglia, amygdala ischemia</td>
<td>53</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>#2</td>
<td>51</td>
<td>F</td>
<td>8</td>
<td>L</td>
<td>Left fronto-temporo-parietal ischemia</td>
<td>45</td>
<td>–</td>
<td>57</td>
</tr>
<tr>
<td>#3</td>
<td>45</td>
<td>F</td>
<td>12</td>
<td>R</td>
<td>Right fronto-temporo-parietal ischemia</td>
<td>51</td>
<td>–</td>
<td>63</td>
</tr>
<tr>
<td>#4</td>
<td>53</td>
<td>F</td>
<td>12</td>
<td>R</td>
<td>Right temporal and basal ganglia haemorrhage</td>
<td>54</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>#5</td>
<td>41</td>
<td>F</td>
<td>8</td>
<td>L</td>
<td>Left-fronto-parietal-rolandic convexity ischemia</td>
<td>77</td>
<td>–</td>
<td>89</td>
</tr>
<tr>
<td>#6</td>
<td>47</td>
<td>F</td>
<td>8</td>
<td>R</td>
<td>Right fronto-temporo-parietal ischemia</td>
<td>44</td>
<td>–</td>
<td>66</td>
</tr>
<tr>
<td>#7</td>
<td>66</td>
<td>F</td>
<td>12</td>
<td>R</td>
<td>Right fronto-temporal-parietal ischemia</td>
<td>50</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>#8</td>
<td>41</td>
<td>M</td>
<td>12</td>
<td>R</td>
<td>Right fronto-temporo-parietal ischemia</td>
<td>49</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>#9</td>
<td>64</td>
<td>M</td>
<td>6</td>
<td>R</td>
<td>Right nucleo-capsular ischemia</td>
<td>46</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>#10</td>
<td>70</td>
<td>M</td>
<td>5</td>
<td>R</td>
<td>Right mca thrombosis with ischemia</td>
<td>78</td>
<td>60</td>
<td>96</td>
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<tr>
<td>#11</td>
<td>54</td>
<td>M</td>
<td>7</td>
<td>R</td>
<td>Right nucleo-capsular, temporal lobe ischemia</td>
<td>76</td>
<td>49</td>
<td>90</td>
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<tr>
<td>#12</td>
<td>70</td>
<td>M</td>
<td>5</td>
<td>R</td>
<td>Left nucleo-capsular, temporal subcortical</td>
<td>46</td>
<td>8</td>
<td>47</td>
</tr>
<tr>
<td>#13</td>
<td>57</td>
<td>M</td>
<td>6</td>
<td>R</td>
<td>Right emi pons ischemia</td>
<td>72</td>
<td>44</td>
<td>78</td>
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<tr>
<td>#14</td>
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<td>M</td>
<td>12</td>
<td>L</td>
<td>Left fronto-temporo-parietal ischemia</td>
<td>72</td>
<td>54</td>
<td>89</td>
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<tr>
<td>#15</td>
<td>64</td>
<td>M</td>
<td>6</td>
<td>L</td>
<td>Left fronto-mesial, insular ischemia</td>
<td>70</td>
<td>37</td>
<td>82</td>
</tr>
<tr>
<td>#16</td>
<td>71</td>
<td>F</td>
<td>6</td>
<td>L</td>
<td>Left emi pons ischemia</td>
<td>72</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>#17</td>
<td>75</td>
<td>F</td>
<td>10</td>
<td>L</td>
<td>Left-cortical-subcortical-fronto-insular, prerolandic ischemia</td>
<td>72</td>
<td>44</td>
<td>75</td>
</tr>
<tr>
<td>#18</td>
<td>58</td>
<td>M</td>
<td>10</td>
<td>L</td>
<td>Semioval center and corona radiata</td>
<td>60</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>#19</td>
<td>34</td>
<td>F</td>
<td>8</td>
<td>L</td>
<td>Fronto-temporinsular cortical-subcortical</td>
<td>43</td>
<td>9</td>
<td>62</td>
</tr>
<tr>
<td>#20</td>
<td>44</td>
<td>F</td>
<td>4</td>
<td>L</td>
<td>Nucleobasal-insular left</td>
<td>41</td>
<td>5</td>
<td>47</td>
</tr>
</tbody>
</table>

Mean 55.5 ± 8.4
St. Dev. 11.9 ± 2.8

F = Female, M = Male, R = Right, L = Left. ESS = European Stroke Scale: the scale ranges from 0 (maximally affected person) to 100 (normal). MRC = Medical Research Council scale for muscle strength, upper limb section: the scale ranges from 0 (no movement) to 5 (complete movement against full resistance) for each segment explored (8 segments per side in the upper limb). FMA = Fugl-Meyer Assessment: scores range from 0 (maximally affected) to 66 (normal); FMA was performed in 14 of the 20 recruited patients.

Fig. 1. Schematic illustration of a representative experimental session. The visual cue is shown on the left side of panels A (task trial) and B (baseline trial). The right side of panels A and B shows the raw EEG signal recorded from a patient performing the motor imagery of the unaffected hand (Uhand). Traces were obtained from C1 electrode position and were relative to a task and a baseline trial. In both cases, the trial duration was 8 s and the period of interest for functional connectivity estimation ranged from the 4th (visual cue onset in task trials) to the 8th (end of trial) second.
frequency domain. This method yields a FC pattern that is not affected by the volume conduction noise due to the anisotropic conductivity of the skull, which blurs the original signals that are generated by the cortical surface. Imaginary coherence gives weighted values between 0 and 1 for each frequency—i.e., higher imaginary coherence values in a frequency reflect greater synchronization between the EEG oscillations at that frequency. The original values of imaginary coherence were then Z-transformed to ensure that they approximated a normal distribution (Nolte et al., 2004).

To study the level of synchronization in specific physiological frequency contents, the Z-transformed imaginary coherence values were averaged within specific ranges, yielding a single mean value that characterized various EEG bands of interest—namely Theta (4–8 Hz), Alpha (8–13 Hz), Beta (13–30 Hz), and Gamma (30–40 Hz). For each patient, run, and frequency band, the connectivity patterns of the MI task segments were contrasted statistically with those of the baseline segments. The statistical comparison was performed over all possible electrode pairs by paired nonparametric Wilcoxon signed rank test, denoted here as W-test.

The functional brain networks that characterized the MI were obtained by maintaining the coherences whose values in the task differed significantly from those at baseline. Similar procedures have been proposed and used in previous studies, in which the functional brain network was the result of a statistical comparison between conditions (Ginestet and Simmons, 2011; Zalesky et al., 2010) or populations (De Vico Fallani et al., 2010). For an analysis of resting states, in which no contrasting procedure is available, the general procedure consisted of repeating the network analysis for a series of increasing threshold settings (Rubinov and Sporns, 2010). The significance threshold was set to \( p = 0.05 \) and adjusted for multiple comparisons by rough false discovery rate (RFDR) correction, based on the number of node pairs for which the W-tests were computed (\( p \) adjusted to 0.025).

Recently, the RFDR criterion has been applied in several neuroimaging studies (Supekar et al., 2008; Wolf et al., 2011).

Network analysis

The estimated FC patterns were characterized using network metrics that have been derived from graph theory (Costa et al., 2011). In our graphs, nodes represent scalp electrodes (\( N = 61 \)) and links represent coherence values between pairs of EEG signals. To eliminate any topological bias due to disparate connection densities between brain networks (van Wijk et al., 2010), we transformed the significant coherence values (from the comparison with baseline segments) into binary values and decreased the links in each brain network to the minimum number that was common to all patients, conditions, and frequency bands.

Thus, the original sparse weighted graphs were converted into unweighted graphs by retaining only the 185 most significant links (\( L = 185 \)) and transforming them into binary values—i.e., \( 0 = \) no link and \( 1 = \) presence of significant link. Although neglecting the weight of the links (i.e., the coherence value) can be considered a reduction of the available information, we noticed that the interpretation and use of link weights in brain network analyses remain a controversial issue, particularly due to the undefined relationship with the concept of physical distance in graphs (Rubinov and Sporns, 2010).

A multiscale topological analysis was eventually applied to the estimated brain networks.

Large-scale properties

Two indices were considered to study the more coarsely grained features of the brain networks—global and local efficiency (\( E_{\text{glob}} \) and \( E_{\text{loc}} \), respectively)—which have been used extensively to characterize the properties of functional brain networks (Bullmore and Sporns, 2012). \( E_{\text{glob}} \) and \( E_{\text{loc}} \) reflect the same properties of the inverse of the average shortest path \( L \) and clustering index \( C \), which were introduced by Watts and Strogatz to characterize the small-world property of networks (see Appendix A for details). A simple measure of efficiency-based smallworldness, \( SW \), can be calculated as \( SW = \frac{E_{\text{glob}}}{E_{\text{glob}}^f} = \frac{E_{\text{loc}}}{E_{\text{loc}}^f} \), where \( E_{\text{glob}} \) and \( E_{\text{glob}}^f \) are the mean efficiency values from equivalent random graphs (Downes et al., 2012). Whenever \( SW > 1 \), a network is considered to exhibit small-world properties.

Intermediate-scale properties

The intermediate-scale level was addressed by examining the properties of 2 predetermined sets of nodes, \( S_{\text{hem}} \) and \( S_{\text{hem}}^f \), which correspond to the scalp sensors of \( A\) and \( U\), respectively (see Appendix A for details).

Interdensity \( K_{\text{inter}} \) is defined as the actual number of links that run between the 2 sets over all possible edges between them. By definition, interdensity ranges from 0 to 1, wherein higher \( K_{\text{inter}} \) values reflect a greater number of interhemispheric links. We considered interdensity to be a particular instance of cut size, a graph index that is used frequently to determine the optimal partition, consisting of separate clusters (see Supplementary Text, Section S1.1).

Intradensity \( K_{\text{intra}} \) is defined as the ratio between the actual number of links in a set and the total number of possible links in the same set. By definition, intradensity ranges from 0 to 1; higher \( K_{\text{intra}}(S) \) values indicate greater connectivity between the nodes in set \( S \).

Small-scale properties

On the small-scale level, we considered graph indices that extracted the finer-grained properties of the EEG network. Two indices were defined to measure the centrality of nodes with respect to the connectivity between and within \( S_{\text{hem}} \) and \( S_{\text{hem}}^f \) (see Appendix A for details). These sets were symmetric and thus had the same number of nodes, \( -N_{\text{hem}} = N_{\text{hem}} = N = 26 \) electrodes.

Interdegree \( D_{\text{inter}} \) was computed as the total number of links of a node in a set to those of the other set. By definition, \( D_{\text{inter}} \) ranges from 0 to \( N \). A node with high \( D_{\text{inter}} \) is considered central, because its removal would reduce overall interhemispheric connectivity.

Intradegree \( D_{\text{intra}} \) was computed as the total number of connections of a node to other vertices in the same group. By definition, it ranges from 0 to \( N \), and a node with high \( D_{\text{intra}} \) is considered central, because its removal would decrease overall intrahemispheric connectivity.

Normalization by random graphs

To handle all normalized network indices, we referred to completely random connectivity patterns, in which links were arranged randomly. Notably, 1000 random graphs were generated by maintaining the same number of nodes and links of the original brain networks. In each instance, links were shuffled randomly without preserving the distribution of node degrees (Sporns and Zwi, 2004). Ultimately, all graph measures that were computed from various brain networks were divided by the respective mean values from the random graphs. When this ratio is lower than 1, the generic brain network property is lower than random graphs; when the ratio exceeds 1, it is higher than random graphs.

Statistical comparison between conditions

We use paired nonparametric Wilcoxon signed rank test (W-test), with a statistical threshold of 0.05, to analyze the differences between brain network indices that were computed for \( A\) and \( U\) conditions (this latter was considered as our reference condition). For small-scale topologies, in which local measures were computed for each node, we corrected for multiple comparisons. Specifically, a nominal significance of \( p = 0.05 \) was defined and adjusted for multiple comparisons by RFDR correction, based on the number of nodes for which the W-tests were computed (\( p \) adjusted to 0.0255). RFDR is a less restrictive procedure for multiple comparisons with greater power than family-wise error rate (FWER) control at the cost of increasing the likelihood of obtaining type I errors (Zar, 1999).
Interscale dependence between brain network properties

In this study, we also examined the dependence of the brain network properties at larger topological scales on those at smaller scales—in other words, small → intermediate and intermediate → large. The linear regression coefficient was computed between the respective network values (independent variables = larger-scale values, dependent variables = smaller-scale values) from all patients under both conditions (Ahand and Uhand) and for each frequency band. Notably, only network attributes that had already reported significant differences between conditions (Statistical comparison between conditions section) were considered for regression analysis. Evaluation of the regression coefficients determined whether and how changes in finer-grained network properties (smaller scale) influence or “possibly cause” (Sokal and Rohlf, 1994) changes in coarser-grained properties (larger scale).

Intrinsic relationships between graph indices

When disparate graph indices are estimated on the same network, they could have a high degree of correlation as a simple consequence of their intrinsic topological definitions—e.g., local efficiency and clustering coefficient (Latora and Marchiori, 2001). In this study, we limited such phenomena by considering graph indices that characterized different scales of topology. Nevertheless, these basic relationships should be determined to interpret the interdependence between changes in graph indices fairly. In general, node degrees (intra/inter) are intuitively related to the connection density (intra/inter)—i.e., a set of nodes with a higher degree indicates greater connection density.

There is a less defined relationship between efficiency values and connection densities. In particular, global ($E_{glob}$) and local efficiency ($E_{loc}$), which reflect integration and segregation tendencies between groups of nodes, respectively, are intended to be related to the connectivity between hemispheres—i.e., $K_{inter}$. To examine this issue, we implemented a simulation model that characterized the dynamics of efficiency-based values ($SW$, $E_{glob}$, $E_{loc}$) with regard to increasing interhemispheric connectivity ($K_{inter}$).

The model generated a sequence of networks that had the same size of the brain networks that were considered here—in other words, $N = 61$ and $l = 185$. Starting from a network configuration in which all 185 links were arranged randomly in 1 hemisphere ($N_1 = 26$ nodes), the model reassigned an increasing number of links between the hemispheres randomly until it reached a configuration that had only interhemispheric links. The choice of such model characteristics was suggested by recent evidence of the effects of stroke on interhemispheric connectivity (Grefkes and Fink, 2011; Westlake and Nagarajan, 2011).

To this end, we hypothesized that the estimated brain networks should lie within a range that is delimited by perfect hemisphere lateralization with respect to sensorimotor control of the contralateral hand (McFarland et al., 2000; Volkman et al., 1998) and abnormal and complete interhemispheric connectivity. Briefly, an increasing number of links $l = 1, 2, \ldots, 185$ was shuffled randomly in the simulation model. Because we did not know the optimal proportion of the $l$ links to be rearranged between the hemispheres a priori, we introduced a parameter, $p_{inter}$, to vary this ratio.

Thus, the simulated network configuration exhibited interhemispheric links that were proportional to $p_{inter}$ and intrahemispheric links that were proportional to $1 - p_{inter}$. When $p_{inter} = 0$, we invoked the inferior limit condition in which the $l$ links were reassigned in only 1 hemisphere. When $p_{inter} = 1$, the $l$ links were rearranged exclusively between hemispheres. To simplify this process, 6 equally spaced $p_{inter}$ values were selected: 0, 0.2, 0.4, 0.6, 0.8, and 1. For each $p_{inter}$ value, 1000 random configurations were generated to obtain proper confidence intervals for the simulation model. More details can be found in Appendix B.

Correlation with functional/clinical measures

Statistical correlations were computed between functional/clinical measures in patients and values of the brain network indices that resulted significant after the Ahand versus Uhand contrast (Statistical comparison between conditions section). Specifically, for those network indices, we considered a delta index ($\Delta$), calculated as the difference between the values for Ahand and Uhand. The $\Delta$ values were then used to determine the correlations with functional scale scores. The nonparametric Spearman correlation coefficient $R$ was used to analyze the statistical dependences. A $p$-level of 0.05 was the threshold for statistical significance. This statistical threshold was initially preferred to an adjusted level for multiple comparisons as we wanted to focus on few planned correlations between the Fugl–Meyer assessment score (FMA), which is specific of the motor function of the patients, and the significant large-scale and intermediate-scale network indices that resulted from Ahand versus Uhand. We are aware that this choice is arbitrary and though it reduces family-wise type II errors, it does not control for family-wise type I errors (Zar, 1999).

Results

Fig. 2 shows the grand average ($n = 20$ patients) of the brain networks in the representative Beta band. Under the Uhand condition (panel A), the overall $FC$ tended to converge on the contralateral (contralesional) hemisphere (Uhemi), primarily over the scalp sensorimotor area (electrode C1). In contrast, we did not observe specular behavior in Ahand (panel B), wherein the FC pattern had a similar distribution in the 2 hemispheres with a relatively high representation of frontoparietal and interhemispheric links (gray lines). This profile was also evident in the bottom section of the same figure, in which $FC$ patterns are represented as graphs. Under the Uhand condition, the brain network (represented as a graph) appeared to segregate into 2 primary clusters of nodes, coincident with the 2 hemispheres. In contrast, a more intermingled structure of connectivity emerged in Ahand.

Multiscale EEG network properties

The analysis for the large-scale topological level was performed by comparing the $SW$, $E_{glob}$, and $E_{loc}$ indices under the Ahand versus Uhand conditions (see Statistical comparison between conditions section). All estimated brain networks tended to have small-world properties—i.e., $SW > 1$ (Fig. 3A). In the Beta band, SW was significantly ($p = 0.025$) lower in Ahand compared with Uhand. Similarly, in the Beta band, $E_{loc}$ under Ahand was significantly ($p = 0.006$) lower than that under Uhand (Fig. 3B). $E_{glob}$ did not differ between conditions in any EEG frequency band (Supplementary Table S1).

On the intermediate-scale level, we compared inter- and intra-hemispheric FC separately between Ahand and Uhand. Interhemispheric connectivity, as measured by the interdensity $K_{inter}$, was significantly higher in Ahand for the Beta ($p = 0.045$) band (Fig. 3C). Consistent with this observation, the tendency of the brain networks to form 2 separate clusters that were coincident with the 2 hemispheres was significantly lower (Beta $p = 0.001$) in Ahand versus Uhand (see Supplementary Text, Section S2.1). In the analysis of intrahemispheric connectivity, the intradensity $K_{intra}$ of the unaffected hemisphere $K_{intra}(Uhemi)$ in the Beta band was significantly higher ($p = 0.009$) in the contralateral Uhand with respect to Ahand (Fig. 3D). A nearly significant difference ($p = 0.051$) was also observed for the $K_{intra}(Uhemi)$ values between the contralateral Ahand and Uhand. No other significant differences were noted for $K_{intra}$ or $K_{inter}$ in the other frequency bands (Table 2).

At the smallest-scale level, the analysis was performed by comparing the interhemispheric and intrahemispheric FC of each scalp site separately between the 2 conditions. In the Beta band, the interdegree
D_{D_{\text{inter}}} of the interhemispheric local connectivity was significantly higher in Ahand versus Uhand for sites PO8 (p = 0.01) and P8 (p = 0.02) in the contralaterally affected hemisphere Ahemi (Fig. 4A). In the same band, in-degree D_{D_{\text{intra}}} of the intrahemispheric local connectivity was significantly higher in Ahand for sites F2 (p = 0.017), F4 (p = 0.027), and P4 (p = 0.016) of the contralateral Ahemi and in Uhand for sites C1 (p = 0.019), CP1 (p = 0.014), CP3 (p = 0.006), and C5 (p = 0.013) of the contralateral Uhem (Fig. 4B).

Few marginal significant differences were noted on the small-scale topological level in the other frequency bands (see Supplementary Text, Section S2.2). We could not exclude that such differences could be affected by false positives as a consequence of the less restrictive procedure used to control multiple comparison (RFDR, see Functional connectivity estimation section). However, these differences were considered to have minor relevance, because no concomitant significant differences were observed at the larger topological scales.

**Influence of smaller-scale on larger-scale network properties**

In the Beta band, in which significant differences between conditions have been reported on each topological scale, we observed a significant negative dependence of local efficiency $E_{\text{loc}}$, on interdensity $K_{\text{inter}} (R = -0.342, p = 0.030)$, which, in turn, depended positively on the degree $D_{\text{intra}}$ of node PO8 in the affected hemisphere Ahemi ($R = 0.415, p = 0.007$) (Fig. 5, lower central region). No significant influence of intradensity $K_{\text{intra}}(\text{Ahemi})$ or $K_{\text{intra}}(\text{Uhem})$ on $E_{\text{loc}}$ was seen (Fig. 5, upper inner left and right regions).

Yet, the intradensities of the 2 hemispheres exhibited a strong relationship with the degrees of specific nodes in the respective hemisphere. In the unaffected hemisphere, a significant positive dependence of $K_{\text{intra}}(\text{Uhem})$ on $D_{\text{intra}}$ of node sites C1, CP1, and CP3 appeared in the regression analysis ($C1 \rightarrow R = 0.475, p = 0.0003; CP1 \rightarrow R = 0.426, p = 0.006; CP3 \rightarrow R = 0.569, p = 0.0001$) (Fig. 5, upper outer left region). Finally, in the affected hemisphere, there was a significant positive dependence of $K_{\text{intra}}(\text{Ahemi})$ on $D_{\text{intra}}$ of nodes F2, F4, and P4 ($F2 \rightarrow R = 0.455, p = 0.001; F4 \rightarrow R = 0.477, p = 0.003; P4 \rightarrow R = 0.547, p = 0.0002$) (Fig. 5, upper outer right region). No other significant relationships were seen.

**Model validation**

Whereas the dependence between node degrees and connection densities was intuitive (ie, higher node degrees contribute to higher connection density), the relationship between interdensity and local efficiency was apparently more complex and therefore examined using the simulation model from Intrinsic relationships between graph indices section. Within the range of values for the model parameter $p_{\text{inter}}$, that controls the proportion of links that are rearranged randomly between hemispheres, we first reported that $p_{\text{inter}} = 0.8$ reproduced the efficiency-based values and interdensities that corresponded to the actual values for the estimated brain networks (see interval of shuffled links between $75$ and $90$ in Fig. S1 and Table S1). Further, in this optimal model configuration and specific interval of redistributed connectivity, the linear increase in interdensity (black line) caused a nearly linear decline in $E_{\text{loc}}$ (red line), whereas $E_{\text{loc}}$ values (blue line) remained stable (Fig. 6). As a consequence,
being the small-world index SW the product of $E_{	ext{glob}}$ and $E_{\text{loc}}$ (see Large scale section), we concluded that the decrease in SW (green line) was due primarily to the fall in $E_{\text{loc}}$. Eventually, by superimposing the average $K_{\text{inter}}$ values for the actual brain networks in the Beta band, we determined that the MI of the affected hand was characterized by greater interhemispheric connectivity and lower local efficiency compared with the unaffected condition.

Correlation with functional/clinical motor scales

A robust statistical correlation was observed between the connectivity of the affected hemisphere in the Beta band and the level of functional/clinical motor impairment of the stroke patient sample, as measured using the Fugl–Meyer Assessment (FMA) scale. Specifically, the FMA correlated positively ($R = 0.53$, $p = 0.045$) with the variation in $K_{\text{inter}}$ in Ahemi between conditions, based on the difference $\Delta K_{\text{inter}}$(Ahemi) (Fig. 3E)—thus, higher FMA values reflected greater $K_{\text{inter}}$(Ahemi) values in Ahand versus Uhand. $\Delta K_{\text{inter}}$(Ahemi) also correlated (not significantly) positively with the European Stroke Scale (ESS) and Medical Research Council (MRC) scale scores (Fig. S2). No other significant correlations were reported.

Discussion

In this study, we demonstrated that EEG-derived brain networks experience specific topological modifications during MI of the affected hand, with respect to the unaffected, occurring primarily within the Beta frequency oscillation (13–30 Hz). Beta rhythms during MI have been correlated to sensorimotor processes in healthy subjects (McFarland et al., 2000) and stroke patients (Gerloff et al., 2006). In the latter, the relative asymmetry between ipsilesional and contralesional hemispheres during contralateral MI and its relationship with functional motor impairment remain debated (Graziadio et al., 2012; Shahid et al., 2010). Here, the involvement of beta oscillatory activity is consistent with its function in the processing of overt and covert motor performance and corroborates previous observations of changes in EEG activity after stroke.

Reduced smallworldness

The recruitment of the affected hand MI was characterized by a significant reduction in smallworldness, SW, compared with the unaffected hand, reflecting a critical deviation from what might be considered optimal brain organization (Gerloff and Hallett, 2010). This decline was concomitant with a decrease in local efficiency $E_{\text{loc}}$ (Fig. 3B), meaning that there was a lower tendency of the network to form tightly knit groups. In the context of networks, the presence of highly connected non-overlapping groups implies that the network divides naturally into sets of nodes with dense connections internally and sparser connections between sets.

Based on the anatomic substrate of the human brain network, comprising 2 predetermined macro groups of regions—i.e., here the affected and unaffected hemispheres—one might wonder to what extent the reduction in local efficiency could be predicted, based on the increase in interdensity $K_{\text{inter}}$ between hemispheres (Fig. 3C) or the decrease in intradensity $K_{\text{intr}}$ within contralateral hemispheres (Fig. 3D). Our regression analysis indicated that the decrease in local efficiency depended significantly on the rise in interhemispheric density, whereas there was no relationship between the changes in intrahemispheric densities (Fig. 5). This dependence was corroborated by the simulation model, which demonstrated that the reduction in local efficiency was caused mechanically by the increase in interhemispheric links (Fig. 6). Thus we hypothesize that the loss of smallworldness (i.e., large-scale attribute) during Ahand was determined primarily by the abnormal rise in connectivity between hemispheres (i.e., intermediate-scale attribute).

Table 3

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<th>$K_{\text{inter}}$</th>
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|       | Uhemi Ahemi       | Uhemi Ahemi       |-
|       | Uhand Ahand       | Uhand Ahand       |-
| Theta | Mean 1.06 0.91    | 0.99 1.04         | 0.93 1.03 |
|       | St. Dev. (0.20) (0.13) | (0.14) (0.25) | (0.2) (0.21) |
| Alpha | Mean 1.16 1.00    | 0.99 0.98         | 0.93 0.99 |
|       | St. Dev. (0.43) (0.16) | (0.16) (0.29) | (0.19) (0.23) |
| Beta  | Mean 1.29* 0.95*  | 0.84* 1.09*       | 0.91* 1.03* |
|       | St. Dev. (0.21) (0.21) | (0.33) (0.29) | (0.22) (0.16) |
| Gamma | Mean 0.87 1.02    | 1.12 1.02         | 0.98 1.05 |
|       | St. Dev. (0.21) (0.13) | (0.17) (0.21) | (0.27) (0.20) |

Standard deviations are reported within parentheses. Asterisks indicate significant differences ($p < 0.05$) between the values of the Ahand and Uhand condition. White circles stand for marginal significantly ($p < 0.05$) different values between Ahand and Uhand.
One of the most common issues after unilateral stroke is how it alters the function of the ipsilesional hemisphere (Greffkes and Fink, 2011; Westlake and Nagarajan, 2011). Compared with the unaffected hemisphere, in which the contralateral MI leads to significantly greater intrahemispheric connectivity with respect to the ipsilateral condition, the affected hemisphere experiences a similar, but weaker, difference between intrahemispheric connectivity that was elicited by the contralateral and ipsilateral MI. This result suggests that some form of hemispheric lateralization was preserved in our sample of subacute stroke patients (1–3 months).

However, whereas contralateral intrahemispheric connectivity depended significantly on the local connectivity ($D_{\text{intra}}$) of the typically involved primary sensorimotor areas in $U_{\text{hand}}$ (McFarland et al., 2000) (Fig. 4B, left hemisphere, and Fig. 6), the contralateral intrahemispheric density depended significantly on the node degrees of the frontal ($F_2$ and $F_4$ matched) and parietal ($P_4$ matched) areas in $A_{\text{hand}}$ (Fig. 4B, right hemisphere, and Fig. 6). Collectively, these findings implicated abnormal recruitment of the cortical regions of $A_{\text{hemisphere}}$ during the respective contralateral MI.

A recent EEG study demonstrated a significant connectivity from the contralateral to ipsilesional sensorimotor cortex in the lower Beta frequency band during movement of a paralyzed hand in less recovered stroke patients (Serrien et al., 2004).

In our study, we observed a significant increase in interdensity $K_{\text{inter}}$ during MI of the affected hand (see Fig. 3C), which depended significantly ($p < 0.01$) on the rise in interdegree $D_{\text{inter}}$ of site PO8 in the ipsilesional hemisphere (Fig. 4A and Fig. 6). This result implicates the contribution of local connectivity between the parieto-occipital region in the affected hemisphere (PO8 matched) and contralateral hemisphere. Whether this outcome reflects a functional reorganization that involves the “intact” hemisphere directly to compensate for the affected sensorimotor cortex is unknown.

Previous studies, based on EEG and MEG recordings, have suggested that Beta synchronous networks that involved the posterior parietal lobe constitute a general mechanism that implements attentional preparation, or readiness (Gross et al., 2004). Thus, the higher interhemispheric connectivity in the parieto-occipital region of the ipsilesional hemisphere could result instead from greater attentional resource engagement for patients during covert motor performance that involves their affected upper limbs. Notably, increased attention on the task has also been postulated to represent a compensatory mechanism in cases of incomplete recovery (Strens et al., 2004).

Abnormal recruitment of the affected hemisphere

For the affected hemisphere ($A_{\text{hemisphere}}$), the imbalance in $K_{\text{intra}}$ between contralateral ($A_{\text{hand}}$) and ipsilateral ($U_{\text{hand}}$) MI was significantly related to the severity of the functional impairment in the upper limb (FMA)—less extensive impairments effected a greater imbalance in favor of the
contralateral MI condition (see Fig. 3E). Such a mechanism could reflect partial preservation of the original hemispheric laterality, similar to what was observed in the unaffected hemisphere (Fig. 3D, left side). Yet, this laterality was less evident in patients with more severe motor impairments, resulting in lower sensibility of the affected hemisphere in recruiting a dense FC in the affected hemisphere in Ahand (Fig. 3D, right side).

This finding points out a potential EEG network-based biomarker for the assessment of cortical plasticity that is related to the degree of motor impairment after unilateral stroke. \( \Delta K_{\text{inter}}(\text{Ahemi}) \) could be used, for instance, to assess functional reorganization of the brain during specific MI-based rehabilitation strategies, such as those that exploit brain–computer interface (BCI) systems, which provide the patient with an online measure of his MI activity and devises appropriate neurofeedback to establish a more ecological and closed-loop neuromotor rehabilitation (Buch et al., 2012; Pichiorri et al., 2011).

**Methodological considerations**

**Task-based connectivity**

Baseline resting states are fundamental in understanding most complex systems (Raichle et al., 2001). The advantages and disadvantages of task-related connectivity with respect to resting-state connectivity in stroke were discussed recently (Westlake and Nagarajan, 2011). Essentially, task-based paradigms elicit brain activity that do not reflect the underlying anatomic structure exclusively, but they can generate many confounding effects that are difficult to isolate (Damoiseaux et al., 2006). In this study, we deliberately chose a specific task paradigm, consisting of the MI of hand grasping. MI has been the focus of many neuroscience groups for its significance in revealing...
the neural substrate of cognitive components of movement (Lotze and Halsband, 2006). Recently, a large debate was developed on the possible function of MI in sustaining motor recovery after stroke, renewing interest on this subject (Ietsonwaart et al., 2011).

Different lesioned hemispheres
One shortcoming of this study is that 9 of 20 patients suffered from lesions to the right hemisphere, whereas the remaining 11 had a left hemispheric stroke. Thus, differences in lesion location might have introduced confounding variables with regard to the common outcome interpretation. To limit this variability, we created a combined group of patients where only their right hemisphere could be considered affected. Although we are aware of the drawbacks of this approach, we report that it is performed frequently to avoid oversegmentation of the study population and create a group of patients that is sufficiently large to provide statistically valid results and conclusions (Luft et al., 2004; Ward et al., 2004). Furthermore, in a separate statistical analysis, there were no significant differences in the Beta band between the left (n = 11) and right hemisphere-lesioned subgroups (n = 9) in terms of network indices under the Ahand or Uhand condition (Table S2).

Unaffected side as control condition
Another issue is related to our experimental design in which we considered the MI task performed with the non-paralyzed hand as a reference condition (Uhand) with respect to our target condition, namely the MI of the affected hand (Ahand). Previous studies have shown the existence of alterations of the unaffected hemisphere motor cortical output after stroke (Shimizu et al., 2002) that however, had little or no influence on functional motor recovery (Netz et al., 1997). In our experimental condition, we assumed that possible pathological changes of the non-affected hemisphere did not generate any functional motor impairments of the contralateral hand as indicated by the functional motor assessment. Bearing in mind that our Uhand condition cannot be a substitute of a normal control condition (i.e., motor imagery performed by healthy age-matched individuals), the robust and sensible differences observed in the brain networks associated with the 2 experimental conditions performed by the same patient are valuable to allow insights into the picture of the brain responses to stroke lesions and their functional relevance.

Subcortical and cortical lesions
To exclude the fact that the obtained results could be somehow influenced by possible EEG signal modifications due to presence of anatomical lesions under the scalp electrodes, we repeated the analysis for the subgroup of subcortical patients (n = 5, see Table 1). Even if the small sample size presented a proper statistical computation, the results obtained for the subcortical group showed a tendency which is similar to what observed in the overall group analysis (see Figs. S3 and S4). More importantly, the remaining subgroup of subcortical and/or cortical patients (n = 15) still exhibited a pattern of significant differences between conditions that is comparable to the results obtained from the entire group of 20 patients (Figs. S5 and S6).

Conclusions
This report is the first advanced network analysis to describe multiscale topological attributes of EEG motor networks in the presence of a unilateral stroke lesion. Compared with the unaffected hand, the MI of the affected hand was characterized by a brain network that displayed lower small-worldness and local efficiency (large-scale attributes) increased interhemispheric connectivity (intermediate-scale attribute), and higher regional connectivity over the frontoparietal areas of the affected hemisphere in the Beta band. Using a simple, but novel, approach we identified the influence of the smaller scale on larger-scale network properties and represented them as a “network of network properties.”

The relevance of our findings seems to be confirmed by the observed correlation between the level of patients’ motor impairments and the connectivity “status” of the affected hemisphere, thus suggesting the presence of a complementary neuromarker that could be monitored throughout longitudinal recording sessions and considered in future motor cognitive-based rehabilitation strategies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.06.039.

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Conflict of interest
We declare no conflict of interest relevant to the contents of this article.

Appendix A. Network analysis
The mathematical representation of a network is a graph. A graph consists of a set of nodes N and a set of links that weigh a certain relationship between vertices. The adjacency matrix A contains information on the connectivity structure of the graph and has dimensions N × N. When a link connects 2 nodes i and j, the corresponding entry of the adjacency matrix is aij = 1; otherwise, aij = 0. In our graphs, nodes represent scalp electrodes (N = 61), and unweighted links represent a significant coherence value between pairs of EEG signals.

A.1. Large-scale indices
Global efficiency and local efficiency are based on the concept of efficiency $e_v = 1 / d_v$, which is the reciprocal of the distance $d_v$, computed as the length of the shortest path that connects 2 vertices i and j (Latora and Marchiori, 2001). A small-world network is characterized by global and local efficiencies that are both relatively higher than random graphs with the same number of nodes and links. Such a configuration is considered optimal in terms of a “perfect” balance between the integration and segregation properties of brain function and efficient communication between brain regions (Tononi et al., 1994). Moreover, initial clinical studies in functional neuroimaging have demonstrated that different conditions or pathologies can alter the optimal small-world architecture of the functional brain network (Achard et al., 2012; De Vico Fallani et al., 2007; Liu et al., 2008; Stam et al., 2007).

A.2. Intermediate-scale indices
Given the adjacency matrix A, the interdensity $K_{inter}$ reads:

$$K_{inter} = \frac{1}{N_5^2} \sum_{i,j \subset 5\, \text{hemispheres}} A(i,j)$$

(A.1)

where $N_5^2$ is the total number of crossing edges between 2 sets of same cardinality $\#(N_5\, \text{hemis}) = \#(N_5\, \text{other}) = N_5$.

[1] ANR-10-IABHU-06. We would like to thank Claudia Di Lanzo for her preliminary computations, Giovanni Tessitore and Roberto Prevete for their supplementary analyses, and Marco Chavez for his useful suggestions on the modeling part. This paper only reflects the authors’ views; funding agencies are not liable for any use that may be made of the information contained herein.

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The intradensity of a set $S$ reads

$$K_{\text{intra}}(S) = \frac{2}{N_S^2 - N_S} \sum_{i \neq j \in S} A(i,j)$$

where $S = S_{\text{hemisphere}}$ or $S_{\text{hemisphere}}$. By definition, the intradensity ranges from 0 to 1. The higher the $K_{\text{intra}}(S)$ is, the more connected the nodes in group $S$ are.

A.3. Small-scale indices

Given the adjacency matrix $A$, the interdegree $D_{\text{inter}}$ of a node $i$ is:

$$D_{\text{inter}}(i) = \sum_{j \neq \text{intra}} A(i,j)$$

where $S = S_{\text{hemisphere}}$ or $S_{\text{hemisphere}}$ and $i \in S$.

Appendix B. Network simulation model

Let $G(N,L)$ be an unweighted and undirected network with $N$ nodes and $L$ links. Divide $G$ into 2 subsets, $S_A$ and $S_B$, consisting of $N_A$ and $N_B$ nodes, respectively, where $N_A + N_B = N$. The objective of the simulation model is to generate a sequence of $L$ network configurations, in which each configuration has a number of links $l = 1, 2, \ldots, L$ that are redistributed randomly within the network. Notably, the probability $p_{\text{intra}}$ that a shuffled link is reassigned between $S_A$ and $S_B$ is given by total number of connections between the subsets and the total number of connections of the entire network, whereas the probability $p_{\text{inter}}$ that the same link is reassigned within 1 of the 2 subsets is given by total number of connections within the subsets and the total number of connections of the entire network.

Without loss of generality, assume that $N$ is even and $N_A = N_B = N/2$. In this simple case, it is easy to prove that $p_{\text{inter}}$ reads:

$$p_{\text{inter}} = \frac{N}{2(N-1)}$$

and the probability $p_{\text{intra}}$ reads:

$$p_{\text{intra}} = \frac{N-2}{2(N-1)} = 1 - p_{\text{inter}}.$$

In our model, we wanted to parameterize $p_{\text{inter}}$ to modulate the amount of shuffled links to be redistributed within and between $S_A$ and $S_B$. Thus, our parameterized probability is defined as:

$$p_{\text{inter}} = \frac{N}{2(N-1)} + c \in \left(0, \frac{N-2}{2(N-1)} \right).$$

It follows from Eqs. (B.2) and (B.3) that when the parameter $c = -N / 2(N-1)$, then $p_{\text{intra}} = 0$ and $p_{\text{inter}} = 1$, meaning that all $L$ links are reassigned randomly only within the 2 subsets; when the parameter $c = (N-2) / 2(N-1)$, then $p_{\text{intra}} = 1$ and $p_{\text{inter}} = 0$, meaning that all $L$ links are rearranged exclusively between the 2 subsets.