CORTEX 64 (2015) 293–309

Available online at www.sciencedirect.com

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Research report

The smarter, the stronger: Intelligence level correlates with brain resilience to systematic insults

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ARTICLE INFO

Article history:
Received 14 May 2014
Reviewed 8 August 2014
Revised 14 September 2014
Accepted 11 November 2014
Action editor Mike Anderson
Published online 2 December 2014

Keywords:
Intelligence
fMRI
Resting state
Graph theory
Brain connectivity
Cognitive reserve
Functional connectivity
Robustness

ABSTRACT

Neuroimaging evidences posit human intelligence as tightly coupled with several structural and functional brain properties, also suggesting its potential protective role against aging and neurodegenerative conditions. However, whether higher order cognition might in fact lead to a more resilient brain has not been quantitatively demonstrated yet. Here we document a relationship between individual intelligence quotient (IQ) and brain resilience to targeted and random attacks, as measured through resting-state fMRI graph-theoretical analysis in 102 healthy individuals. In this modeling context, enhanced brain robustness to targeted attacks (TA) in individuals with higher IQ is supported by an increased distributed processing capacity despite the systematic loss of the most important node(s) of the system. Moreover, brain resilience in individuals with higher IQ is supported by a set of neocortical regions mainly belonging to language and memory processing network(s), whereas regions related to emotional processing are mostly responsible for lower IQ individuals. Results suggest intelligence level among the predictors of post-lesional or neurodegenerative recovery, also promoting the evolutionary role of higher order cognition, and simultaneously suggesting a new framework for brain stimulation interventions aimed at counteract brain deterioration over time.

1. Introduction

Intelligent people live longer (Deary, 2008). The initial surprise about such a linear relationship between intelligence and life expectancy/mortality has been replaced by several evidences confirming that health inequality partly depends by the individual intelligence level (Batty, Shipley, Gale, Mortensen, & Deary, 2008; Batty et al., 2009). Several factors might account for this interaction, such as the association between early-life intelligence and higher levels of education/professional occupations, or the tendency to pursue in more healthy habits in

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http://dx.doi.org/10.1016/j.cortex.2014.11.005
0010-9452/

terms of sports, smoking, dietary regime and weight control. Furthermore, the correlation between intelligence quotient (IQ) and mortality has been also considered a reductive argumentation respect to a broader biological theory suggesting its relationship with the "overall system integrity", thus implying a "more intelligent" brain to be associated to a likewise well-functioning body, thereby increasing the probability of a longer life (Deary, 2008; Deary & Der, 2005).

On the other side, in the last decade the concept of cognitive reserve (CR) has been introduced (Stern, 2009), as a framework specifically addressing the individual variability between expected and actually observed cognitive capacities across pathological brain conditions like cerebrovascular disease (Murray et al., 2011), Parkinson's disease (Poletti, Emre, & Bonuccelli, 2011) and multiple sclerosis (Langdon, 2011), as well as in healthy elderly subjects with brain atrophy (Stern, 2002). Interestingly, the CR model mainly concerns higher order cognitive functions which pertain to the general intelligence factor "*g*", hence promoting the idea of intelligence as a "buffer" helping to assure a more favorable disease outcome in case of brain pathology (Satz, Cole, Hardy, & Rassovsky, 2011).

Despite the amount of data sustaining the CR model, whether intelligence should be considered just as a tool to indirectly achieve a longer life expectancy, or it must be conceptualized as a functionally relevant phenotype -that is, expression of a cognitively optimized brain towards aging itself or intercurring neurological insults-is still a matter of debate. Consequently, the current study is aimed at investigate the hypothesis that a higher IQ translates into a functionally more resilient brain towards physiological aging or pathology-related loss of regional efficiency, defining "robustness" in the context of a graph-topological analysis already used to characterize complex networks behavior at several biological levels (Albert, Jeong, & Barabasi, 2000).

Recent neuroimaging evidence has suggested how the human brain is a complex system of interconnected regions spontaneously organized into distinct networks (Achard & Bullmore, 2007; Craddock et al., 2013; Fox et al., 2005; Hagmann et al., 2008; Shehzad et al., 2014; Sporns, Tononi, & Edelman, 2002), with such organization being highly correlated with individual differences in manifest behavior, also including complex phenotypes like intelligence (Santarnecchi, Galli, Polizzotto, Rossi, & Rossi, 2014; Van Den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Moreover, brain modeling based on graph-theory allowed to describe such complex organization using indexes referring to notable complex networks properties (Sporns, 2014), like their capacity for simultaneous local and distributed information processing (Eguiluz, Chialvo, Cecchi, Baliki, & Apkarian, 2005; Sepulcre et al., 2010), their organization into separate but integrated modules (Achard & Bullmore, 2007; Sporns, 2013), and their power-law distribution of network nodes importance (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006). Notably, this topological organization, shared by several complex biological systems, often corresponds to an increased "robustness" (or resilience) against system failure [i.e., random error (RE)] or deliberated lesioning procedures [targeted attacks (TA)] (Albert et al., 2000; Bak & Paczuski, 1995; Kitano, 2004). By providing an estimation of the residual network functionality after complete or partial lesions, network simulations allow to infer the response of a complex system to both random or TA, thereby allowing a quantification of complex networks' "goodness" and of their rate of survival against unexpected system malfunctioning. Assuming such network robustness as a "dominant" trait, whether intelligence is associated with such trait is an unexplored argument of absolute interest, including possible implications as to the evolutionary role of human higher order cognition.

We therefore estimated brain functional robustness towards both RE and TA in a group of 102 healthy subjects (49 males, average age = 34 yrs, SD = 14, range 20–60), in the attempt to address the following issues: *(i)* does a higher intelligence profile level correspond to a more robust brain? If so, *(ii)* which are the brain regions more or less susceptible to TA or RE? *(iii)* Given the different neurobiological meaning of RE and TA, is there a specific relationship between intelligence and these two brain robustness indexes? Finally, *(iv)* given the theoretical yet practical differences between crystallized (Gc) and fluid intelligence (G*f*) abilities -respectively representing education-related and more innate "on the spot" cognitive abilities (Nisbett et al., 2012) – do both equally contribute/correspond to such robustness?

2. Materials and methods

Specific details about the cognitive measures and fMRI preprocessing are included as supplemental material and methods. The following sections cover the details about brain resilience computation including networks definition, lesioning process and statistical analysis.

2.1. *Sample and behavioral measures*

Behavioral and neuroimaging data are part of the freely-available NKI-Rockland database, belonging to the FCP/INDI sharing initiative (www.fcon_1000.projects.nitrc.org), including a phenotypic characterization of 207 healthy subjects (age range 4–85 years), as well as structural (anatomical and Diffusion Tensor Imaging – DTI) and functional (resting-state fMRI) neuroimaging data. Considering our aim to characterize a possible link between individual brain robustness and intellectual level, a first concern has been to avoid conditions where an additional modulation of these two factors might be present. Thus, we decided to circumscribe our analysis to adult subjects (20 > sample < 60 years), limiting the effect of developmental and aging-related changes of both cognitive and cerebral architecture. A further selection of subjects was performed to ensure *(i)* an equal number of males and females, given the evidence of interactions between gender and intellectual abilities (Haier, Jung, Yeo, Head, & Alkire, 2005; Payton, 2009), *(ii)* an equal distribution of age groups (decades) within the overall group and *(iii)* that all subjects were right-handed. The selection resulted in a final sample of 102 right-handed subjects (49 males), with mean age of 34 years (range 18–60, SD = 14) and available IQ scores representing overall (Full-scale) IQ as well as verbal and visuospatial IQ scores, respectively considered as indexes of Gc and G*f*.

2.1.1. Network lesioning procedure

Network nodes were defined by parcellating the brain into 90 cortical and subcortical ROIs according to the Automatic Anatomical Labeling atlas (AAL) (Tzourio-Mazoyer et al., 2002), one of the most commonly employed atlas for network analyses (Achard & Bullmore, 2007; Achard et al., 2006; Liu et al., 2008; Wang, Li, Metzak, He, & Woodward, 2010). Details about thresholding and sparsity have been included in the supplemental methods section. For the sake of readability, all the fMRI preprocessing, networks definition and thresholding, graph-theoretical metrics computation and lesioning procedures are schematized in Fig. 1.

As suggested in the introduction, robustness estimation comprehended two approaches for network lesioning, based on random or targeted node removal. These procedures involve the calculation of several topology indices, both for guiding the depletion process itself and for the estimation of network "well-being" after each depletion, whose explanation requires to assume: (*N*) as the set of all nodes in the network, (*n*) as the number of nodes, (*k*) as a specific node, (*L*) as the set of all links in the network, (l) as the number of links, (*i*, *j*) as the link between nodes *i* and *j*, (a_{ij}) as the connection status between *i* and *j* ($a_{ij} = 1$ when link *i*, *j* exists; $a_{ij} = 0$ otherwise). All the graph properties have been calculated using Matlab functions included in the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/). As suggested in the previous section, individual functional connectivity matrices have been thresholded by selecting a progressively larger portion of all possible brain connections, leading to the creation of one hundred different sparsity matrices for each subject. Considering that each lesioning simulation comprised 90 depletions (see Fig. 1B), and that it has been performed on each sparsity matrix, the overall lesioning process resulted in 90 [depletions] * 100 [sparsity matrices] * 102 [participants] simulations, separately for TA and RE.

2.1.2. TA and RE

The purpose of TA procedure is to test the specific importance of certain network nodes for overall network stability. Usually, nodes removal follows a specific order which reflect the nodal properties of interest, for instance its importance for distributed information processing, local computation or modularity of the system. Previous studies about brain robustness have focused on different nodal properties, suggesting "centrality" measures as those providing the best robustness estimation (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009). Well-known measures of centrality are the (*i*) degree, *D*, and the (*ii*) betweenness centrality, *Bc*: while the *D* of a node *k* is the number of edges connecting it to other nodes, so that largely connected nodes show higher degrees, *Bc* is expression of the number of shortest node-to-node paths that pass through a specific node *k*, indicating how such node takes part into overall brain information processing by supporting other nodes communication through fast (i.e., short) connections. Even though there are evidences suggesting *Bc* as the best estimate of centrality for network robustness simulation (Alstott et al., 2009), we also computed the results defining the target nodes by using two additional criteria, i.e., the nodal degree and strength of functional connectivity. Results obtained using these indexes are reported in Fig. S6. Therefore, *Bc* for the node *i* has been defined as:

$$bc_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h,j \in N \\ h \neq j, h \neq i, j \neq i}} \frac{\rho_{hj}(i)}{\rho'_{hj}}$$

where ρ_{hj} is the number of shortest paths between *h* and *j*, and ρ_{hj} (*i*) is the number of shortest paths between *h* and *j* that pass through *i*. As shown in Fig. 1B, the lesioning process consisted in the (*i*) estimation of centrality values for each node of the AAL atlas (say *Bc*), (*ii*) sorting of nodes based on their *Bc* value, (*iii*) removal of the node with higher *Bc* value. This process is recursively applied since all the nodes have been deleted, leading to the progressive creation of 90 matrices (one for each AAL atlas region).

Differently, REs are thought to simulate a completely different phenomenon, which may affect complex network, i.e., the occurrence of a system failure. Random in nature, this event may cause or not a severe impairment to system integrity depending on which nodes is being involved. RE are conducted by (*i*) creating a 1 * 90 vector of randomly selected regions, and by lesioning the network by cutting the node corresponding to position (1,1) in the vector. A new 1 * 89 random vector (containing all regions except for the already cut node) is then created and the process continues till all nodes have been removed. To ensure a more reliable estimation we performed the entire process 100 times for each matrix and averaged the resulting robustness estimates.

Theoretically, the intrinsic structure of complex networks following a power-law degree distribution, like the human brain, guarantees a higher protection towards RE, by concentrating the very large part of information processing on a limited number of core regions which, in terms of probability, are supposed to be more difficult to be affected by a random attack. On the other side, TA are thought to be more effective in networks following such distribution, with even a few surgically planned resections capable to generate highly significant network impairment.

2.1.3. Network integrity against attack

Before the overall process, and between each node(s) depletion, several indices of network integrity are calculated, so that a "time course" of brain robustness is obtained while all atlas regions are progressively removed. Such process allows to identify critical point(s) when the robustness level drops dramatically, which correspond to the specific removal of a single or a small set of brain regions. We calculated measures describing both integration and segregation of functions within the brain, aiming at caughting the impact of network lesioning on (*i*) distributed and (*ii*) local processing. Regards *distributed processing*, two indices were computed, namely the Largest Connected Component – *LCC* and the Global efficiency – *E*. The *LCC* is the typical index usually applied for complex networks robustness estimation (Albert et al., 2000; Alstott et al., 2009). Basically, it reflects the overall network "connectedness", that is the rate at which is possible to directly or indirectly connect each node in the network to each other. Perfectly connected networks, where all nodes are linked to each other forming a unique *component*, naturally

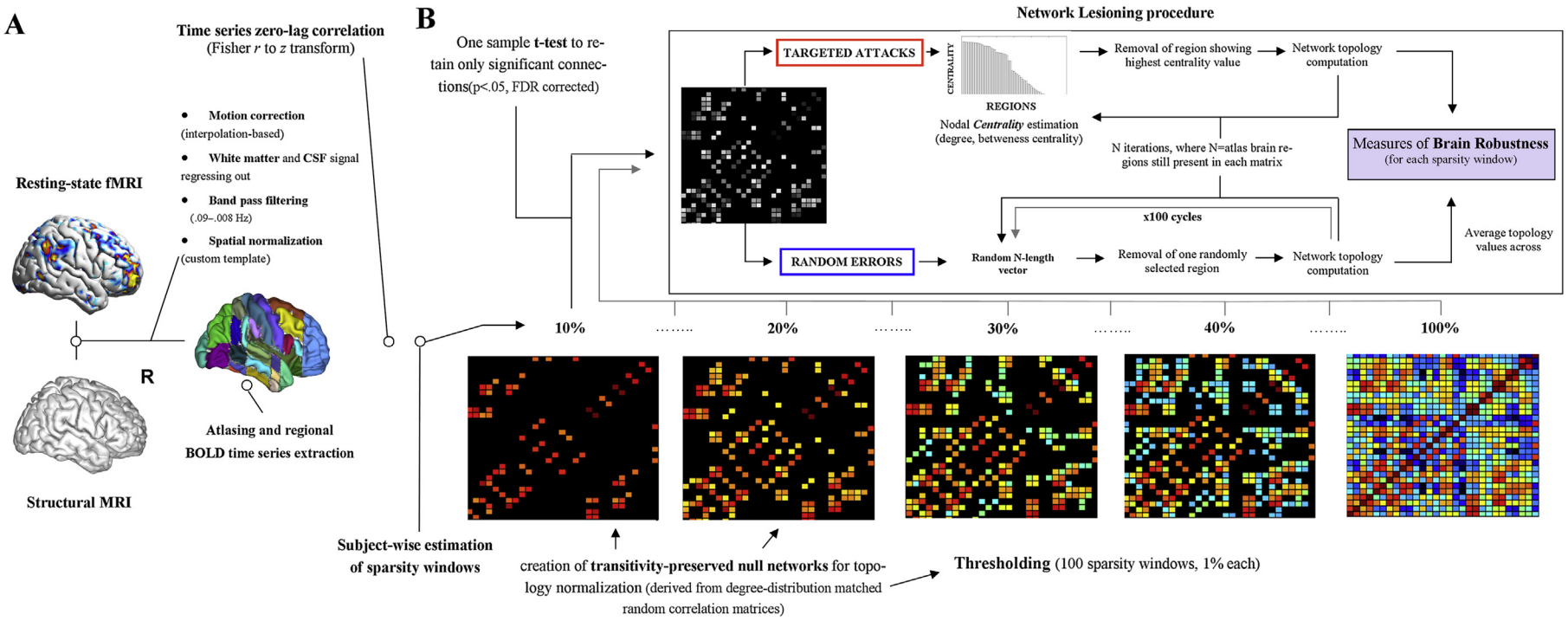

Fig. 1 – Functional MRI preprocessing and graph-topological brain resilience analysis workflow. Schematic representation of the major steps for brain resilience estimation, involving images preprocessing, thresholding procedure based on connectivity strength and topology indices computation. Panel A: functional images underwent canonical preprocessing involving two different approaches for motion correction, removal of possible confounding factors related to breathing and cardiac signals, temporal band-pass filtering, coregistration and spatial normalization using the DARTEL module for SPM. The Anatomical Labeling Atlas (AAL) was used for resting-state parcellation into regions of interest and consequent BOLD signal time series extraction. In order to retain only significant connections (Panel B, upper line), a one-sample t-test was applied over individual connectivity matrices obtained during the thresholding process ($n = 100$), which has been computed for the entire sparsity range (1–100%) using 1% sparsity steps. Matrices followed two separated workflows for Targeted Attacks (TA) and Random Error (RE) simulations. In order to normalize graph topology indices (Panel B, lower line), a Hirschberger-Qi-Steuer algorithm was used to create transitivity-preserved null networks based on random correlation matrices matched for degree-distribution. All steps were performed at the single subject level. Additional details about topology indices estimation and lesioning procedure are provided in supplemental methods.

guarantee a higher level of information spreading. However, complex network usually show a subset of nodes which play a crucial role for maintaining the network "connected", so that their depletion cause most severe damage to the overall network integrity by making a large number of other nodes "unreachable", i.e., disconnected from the component. Thus, *LCC* is defined as the largest number of nodes constituting a component after each depletion, and calculated through the estimation of a distance matrix – *d*, whose *ij* values represent the shortest path length (or distance) between all pairs of nodes, computed as:

$$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv'}$$

with $g_{i \leftrightarrow j}$ representing the shortest path between nodes *i* and *j* (disconnected pairs = ∞). Each cell within the resulting matrices represents the minimum number of steps (node-to-node connections) required to connect each pairs of nodes, so that a (*i*,*j*) blank cell indicates the impossibility to directly or indirectly connect node *i* and *j*. Consequently, higher *LCC* values represent higher levels of connectedness.

Network *E* is defined as:

$$E = \frac{1}{n}\sum_{i \in N} E_i = \frac{1}{n}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^{-1}}{n-1},$$

At a neurophysiological level, high *E* network is guaranteed by nodes placed at short distances from each other, a configuration which enables them to interact more directly, i.e., faster, consequently promoting high functional integration. In this context, higher values of *E* represent better overall brain information processing. Despite one of the most used network integration measures is the average path length, representing the average number of steps along the shortest paths for all possible pairs of network nodes, here we preferred *E* because of its lower sensitivity to the presence of disconnected or very weakly connected nodes (Bullmore & Bassett, 2011; Sporns & Zwi, 2004).

Differently, *local processing* is expression of adjacent neuronal population synchronization, a functional prerequisite for several cognitive functions within the motor, visual, somatosensory and also memory domains (Sepulcre et al., 2010). Here we characterized brain segregation using the Local efficiency index – E_{Loc}, a measure of the average efficiency within local subgraphs or neighborhood. E_{Loc} has been calculated as follow:

$$E_{loc} = \frac{1}{n}\sum_{i \in N} E_{Loc,i} = \frac{1}{n}\sum_{i \in N} \frac{\sum j,h \in N, j \neq i a_{ij} a_{ih} \left[d_{jh}(N_i)\right]^{-1}}{k_i(k_i - 1)}$$

where $E_{Loc,\ i}$ is the local efficiency of node *i*, and $d_{jh}(N_i)$ is the length of the shortest path between *j* and *h*, that contains only neighbors of *i*. Higher level of E_{Loc} represent better information processing at local level.

Furthermore, other topological indexes have been computed in order to determine the individual small-worldness window (SW) where the robustness indexes have been extracted. First of all, SW has been calculated as:

$$S = \frac{CC/CCrand}{L/Lrand}$$

where *CC*-CC_{rand} and *L*-L_{rand} respectively represent the clustering coefficients (*CC*) and the characteristic path lengths (*L*) of the actual network and of a random network ($_{rand}$). The *average path length*, *L*, is defined as:

$$L = \frac{1}{n}\sum_{i \in N} Li = \frac{1}{n}\sum_{i \in N} \frac{\sum j \in N, j \neq i dij}{n-1}$$

where L_i is the average distance between node *i* and all other nodes. It represents the average number of steps along the shortest paths for all possible pairs of network nodes. As an index of information processing efficiency, shorter *L* values usually stand for more efficient networks. The *clustering coefficient*, *CC*, is defined as:

$$CC = \frac{1}{n}\sum_{i \in N} CCi = \frac{1}{n}\sum_{i \in N} \frac{2ti}{ki(ki-1)'}$$

where CC_i is the clustering coefficient of node *i* ($CC_i = 0$ for $k_i < 2$). *CC* is expression of each node's tendency to cluster with neighboring nodes and is thus considered a reliable index of network local connectivity. The individual SW window was composed by those matrices showing a Small-world value >1 (Humphries & Gurney, 2008). Compatible with what previously reported, our sample shows network densities corresponding to SW ranging, on average, from 10 to 31% (Fig. 2B).

2.2. Statistical analysis

Statistical analyses were carried out over all topological measures (*LCC*, *E*, E_{Loc}, *Bc*), even though the main outcome of interest was composed by *LCC* as a direct expression of brain integrity after each node removal (Alstott et al., 2009). We first conducted a linear regression analysis to assess the relationship between IQs (FSIQ, VIQ, PIQ) and the average topological properties of all the matrices corresponding to the small-worldness window of each subject (Humphries & Gurney, 2008). Average values for each network property (*LCC*, *E*, E_{Loc}, *Bc*) have been inserted as independent variables, while IQs scores have been separately included as dependent variables. Furthermore, given the results of regression analysis, an Analysis of Covariance (ANCOVA) specifically contrasting the *LCC* values of High and Low-IQ subjects within the small-world window was computed, including age, Body Mass Index (BMI), total brain volume (TBV) and gender as covariates. An alpha = .05 was chosen as significance level for all the analyses, post-hoc comparisons have been computed using Bonferroni correction ($p < .05$).

The ANOVA has been also used in order to verify the existence of significant between-groups differences in the distribution of *LCC* values as a function of age and intelligence. *LCC* values computed within the small-world window have been thus inserted as dependent variables, with Group (High and Low-IQ) and Decades as independent variables. Specifically for this analysis, a subgroup of subjects belonging to the 61–70 yrs decade has been included in the sample, resulting in 5 decades (21–30 yrs, 31–40 yrs, 41–50 yrs, 51–60 yrs, 61–70 yrs). Moreover, given an *a priori* knowledge about a potential role for brain weak connections into discriminate subjects with High and Low IQ (Santarnecchi et al., 2014), topological measures and robustness indexes have been also

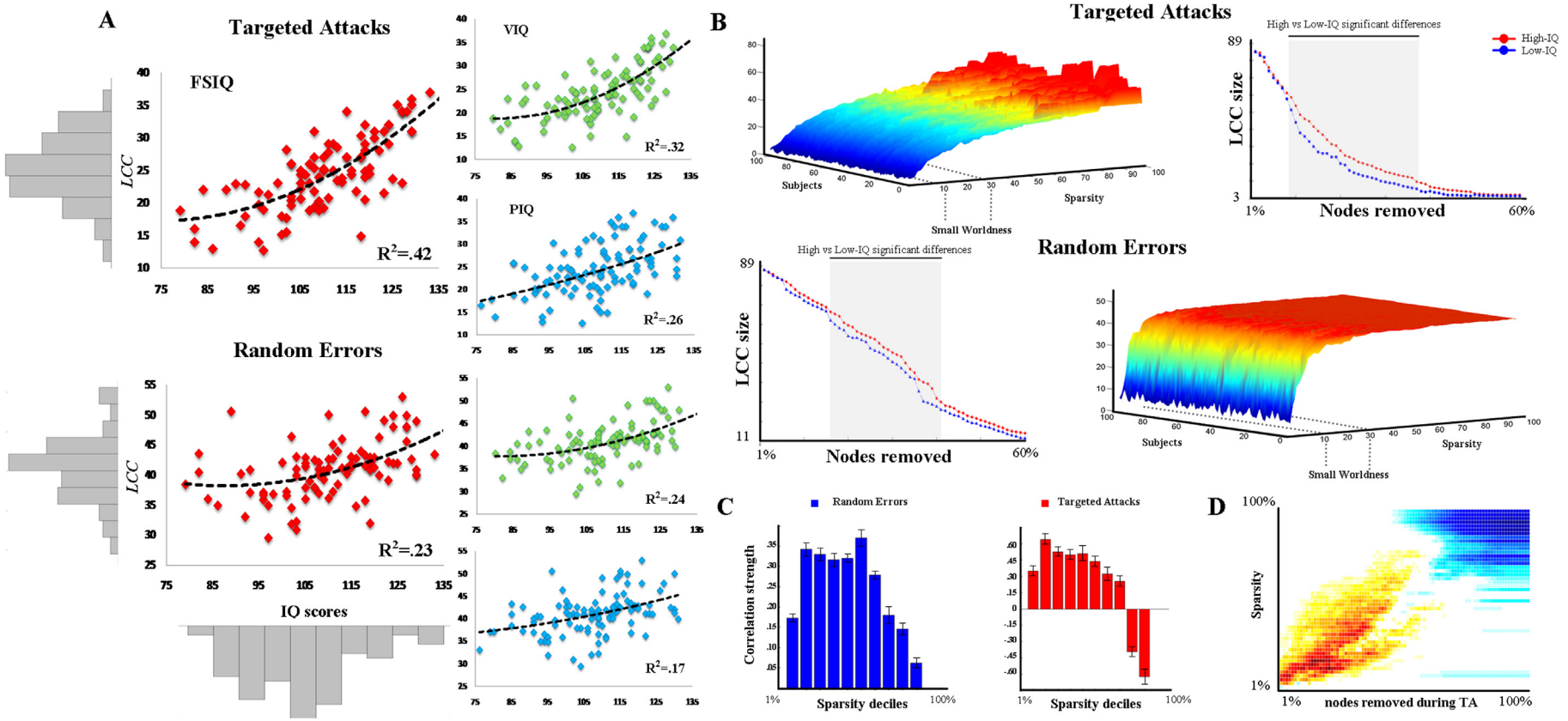

Fig. 2 – Brain Robustness and Intelligence correlation. Panel A: correlations between Full-scale (FSIQ), Verbal (VIQ) and Performance (PIQ) Intelligence Quotients (obtained at the WASI test, *x* axis) and brain robustness to TA and RE, expressed as the average size of the largest connected component (LCC, *y* axis) in the network after a the lesioning procedure. Histograms (in grey) represent data distribution in the overall sample for FSIQ, as well as *LCC* values, for both TA and RE simulations. Panel B: the lesioning procedure has been computed within the entire sparsity windows, by retaining an increasing percentage of all possible connections in a decreasing-strength fashion, thus ranging from 1% (absolute stronger connections) to 100% (*x* axis). However, as commonly applied for graph-theoretical analysis, correlations with IQ scores have been performed by using connectivity data within each subject's small-world sparsity window (group average = 10–31%). Therefore, scatterplots in A and line plots in B refer to the *LCC* size calculated within such window, while surface plots in B, as well as data in C and D, display results for the entire sparsity range. As visible in the surface plots, *LCC* values for TA and RE follow different distributions along the sparsity windows, showing most of the individual differences within the low-sparsity range for RE and 70–90% window for TA. As shown in C (data are grouped into sparsity deciles), this produces different correlation patterns for the two robustness indexes, with an opposite pattern of correlation (Pearson's product–moment correlation coefficient) for the last two sparsity deciles during TA simulation, an effect which is mostly driven by the inclusion of brain weak connections. At a higher resolution level, panel D shows positive (red) and negative (blue) correlations between intelligence quotients and *LCC* as a function of sparsity and % of nodes removed from the network.

computed outside the SW window, that is along the entire sparsity range (1–100%). The same regression model has been than calculated by including progressively weaker connectivities (1% sparsity steps), looking for potential interactions between intelligence and robustness values derived from connectivity matrices including strong, other than weak connections.

2.3. Definition of robustness-related brain regions

Along with the identification of an intelligence-brain robustness interaction, we also aimed at identifying the importance of specific anatomical regions for the maintaining of brain integrity. Consequently, we performed a multivariate classification procedure to assess the contribution of each AAL atlas region to the significant difference in brain robustness to TA observed between High and Low-IQ groups. Assuming the *LCC* as the primary index of interest, a vector of the drop in *LCC* size after each region removal has been created (focusing on individual SW windows) for each subject, resulting in a 102 × 90 matrix. Using Weka software (Frank, Hall, Trigg, Holmes, & Witten, 2004), a support vector machine (SVM) algorithm was tested through leave-one-out cross-validation (folds = 101), resulting in an estimation of the overall correct classification percentage (Sensitivity, Specificity, area under the ROC curve) as well as to a node specific discriminative weight as expression of each region contribution to the overall classification process. However, as the pattern obtained through SVM classification is multivariate, regions above the 95th percentile and below the 5th percentile have been assumed as representing, respectively, brain regions more sensitive to the lesioning process in the High and Low-IQ groups – that is those regions whose removal strongly affect brain integrity by significantly decrease the size of the *LCC* (Santarnecchi et al., 2014). Images were plotted on an inflated three-dimensional brain (Fig. 3), with this graphical representation showing only the regions that carry most of the discriminative weight – that is, those relatively more important to forming the decision boundary.

Furthermore, the identification of the most important regions for the observed intelligence–robustness interaction allows for the investigation of node-specific features supporting such relationship. Therefore, both *(i)* pairwise functional connectivity and *(ii)* seed-to-networks analyses have been computed for all the aforementioned regions. Briefly, functional connectivity has been computed-at the single subject level-as the Pearson correlation coefficient between the time series of all the regions included in the AAL atlas. Differences in the average pattern of connectivity at the group level (High *vs* Low-IQ) have been calculated using a False Discovery Rate (FDR) ($p = .05$) correction, highlighting increase and decrease in the strength of specific connections between each region and the rest of the brain.

At the network level, the average time course of BOLD fluctuations within specific resting-state networks (RSNs) of interest have been extracted, thus representing the average connectivity pattern of such networks in individuals with High and Low-IQ scores. Consequently, correlation values between RSNs time courses and those of the most discriminant regions have been compared across groups ($p < .05$, Bonferroni corrected), highlighting specific intelligence-related relationship between such regions and specific networks. RSNs have been defined as the results of previous investigations (Allen et al., 2011; Mantini, Perrucci, Del, Romani, & Corbetta, 2007), resulting in the definition of nine well-known networks: default-mode, fronto-parietal control, frontal attention, language, somatomotor, auditor, visual and (right-left) working memory networks.

3. Results

A synthetic scheme of the overall procedure for functional connectivity estimation and network lesioning is reported in Fig. 1. It is noteworthy that, given the limitation of available neuroimaging database in terms of sample size and thus age distribution per decade, our approach is aimed at identifying a relationship between intelligence and brain resilience regardless of age, therefore all analyses have been computed including age as a covariate. However, given the potentially relevant role of age for future investigations about brain robustness, an additional exploratory analysis of the age * intelligence * robustness interaction has been completed on the available data and included as part of the supplementary materials. Moreover, in order to rule out the role of brain reserve in such relationship, individual TBV was regressed out from the analysis as well. Additional details about data preprocessing and network analysis are included in the experimental procedures section and supplemental information.

3.1. Correlation between intelligence and brain resilience

Significant correlations between brain robustness and Full Scale, Verbal and Performance IQ scores emerged (Fig. 2A). Even though these correlations were present for both resilience indexes and all IQ scores, a pattern of significantly stronger correlation between the robustness towards TA – expressed as the size of the largest connected component (*LCC*) (Albert et al., 2000) – and FSIQ [$r_{(101)} = .65$, $p < .001$, $R^2 = .42$], VIQ [$r_{(101)} = .57$, $p < .01$, $R^2 = .32$]and PIQ [$r_{(101)} = .53$, $p < .01$, $R^2 = .26$]respect to the impact of RE [FSIQ, $r_{(101)} = .45$, $p < .001$, $R^2 = .12$; VIQ, $r_{(101)} = .47$, $p < .01$, $R^2 = .14$; PIQ, $r_{(101)} = .41$, $p < .01$, $R^2 = .15$] emerged (results for other indexes of distributed and local information processing are included as Supplemental Results). The computation of brain robustness as a function of network sparsity allowed addressing potential differences in the size of the *LCC* across network densities, and thus to evaluate the impact of such network thresholding-dependent procedure on robustness estimation. As previously reported (Achard & Bullmore, 2007; Watts & Strogatz, 1998; Wu et al., 2013), valid arguments sustain the *a-priori* computation of network topology (and robustness) within specific network density windows, mainly focusing on brain properties obtained by looking at network configurations resembling the so-called small-world (SW) topological organization (Fig. 2B) (Achard & Bullmore, 2007). Therefore, the results of statistical models computed within the SW window have been considered the main outcome of interest. However, TA and RE simulations produced strongly different

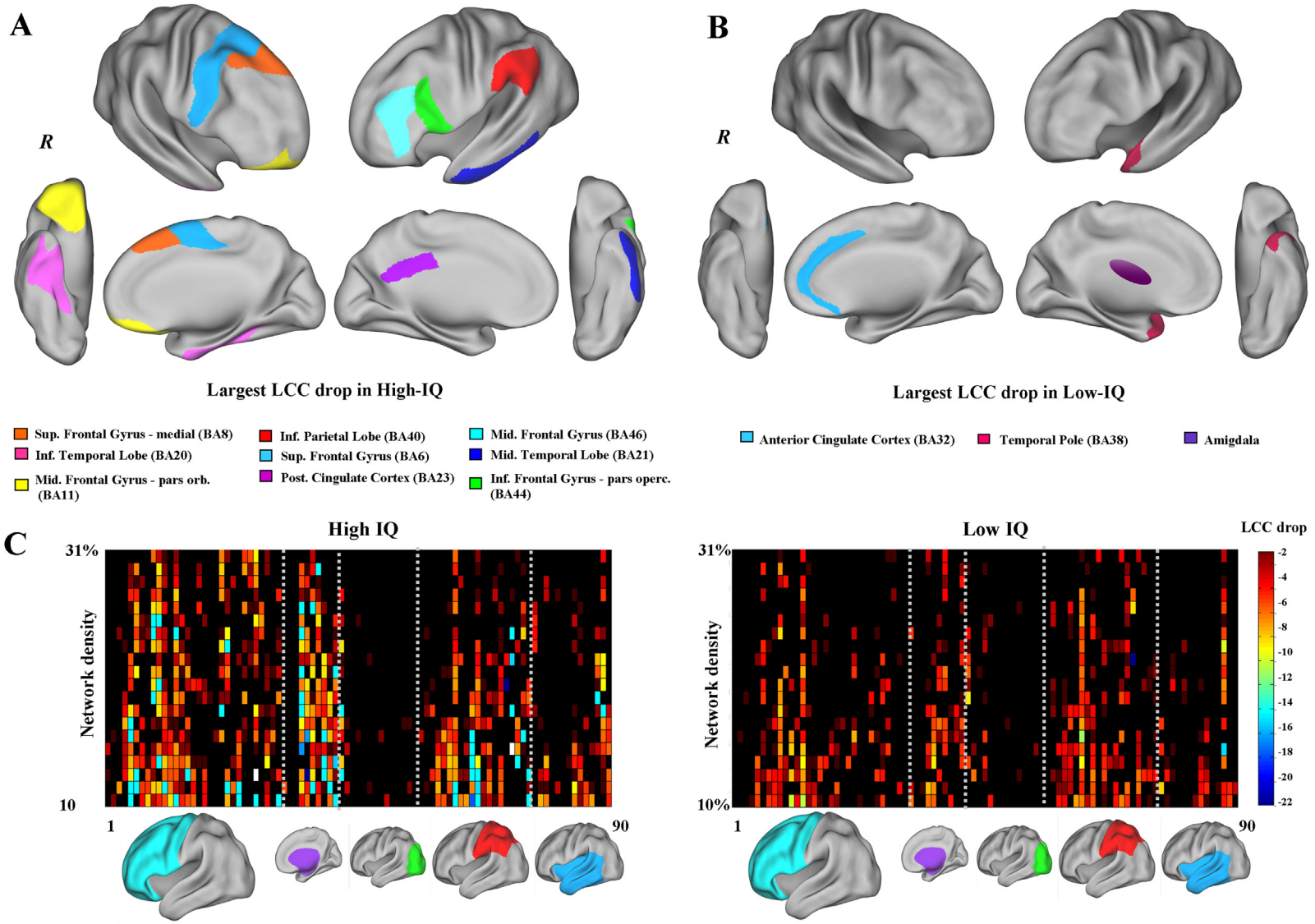

Fig. 3 – Brain Regions responsible for robustness differences. Panel A shows brain regions responsible for higher robustness in High- versus Low-IQ participants during TA simulation, as identified by using support vector machine classification. These regions, mainly represented in the bilateral frontal, parietal and temporal lobes, contributed the most in the drop of robustness (decrease in the size of the *LCC*) after their removal from the network, with an average drop in *LCC* size equal to 14 nodes. Conversely, a smaller set of regions was also identified as responsible for a greater drop in robustness in Low-IQ participants versus High-IQ ones (B). Moreover, a plot of the average drop (see colorbar) for each brain region of the AAL atlas (*x* axis) across the small-worldness sparsity range (*y* axis) is provided in panel C separately for the two groups. Accordingly to panel A, regions belonging to frontal, temporal and parietal lobes (mostly resembling the P-Fit model of intelligence) vehicle the most important robustness-related connections in subjects with higher intelligence quotients.

estimation of brain robustness in respect to the percentage of nodes that were included in the network (Fig. 2B). Accordingly, panel C highlights how the intensity of the correlation with intelligence scores fluctuates as a function of network sparsity, with potential opposite results for TA when weak brain connections are taken into account (sparsity 80–100%). Results related to other network topological properties are included as supplemental results.

3.2. *Identification of resilience-related brain regions*

By investigating the topological features responsible for the observed intelligence-related difference in robustness towards TA, we focused on the identification of those regions whose exclusion from the network lead to the larger loss of brain robustness. Therefore, by applying a median split segmentation of the entire sample we obtained two groups representing participants with High ($n = 57$; mean age = 35 ± 12; mean FSIQ = 119 ± 7) and Low ($n = 45$; mean age = 36 ± 10; mean FSIQ = 84 ± 5) IQ levels (Table 1), with no differences for age ($t = .345$, $p = .534$) and gender distribution ($\chi^2 = .403$, $p = .546$). The analysis of the regions mostly responsible for the intelligence–robustness interaction was carried out by means of a SVM classification procedure, leading to an IQ-groups classification accuracy of 82,7% (CI = .645–.876; Sensitivity = .712; Specificity = .867; AUC .912). The distribution of the differences in the average *LCC* drop for each single region of the AAL atlas used to inform the SVM algorithm is included in Fig. S3. Control analysis using SVM on those regions identified as the most important into separating High and Low IQ participants (12/90) led to an IQ-group classification accuracy of 75,3% (CI = .612–.798; Sensitivity = .689; Specificity = .833; AUC .856). Among High-IQ subjects, these regions mostly belonged to a bilateral network encompassing regions anatomically and functionally crucial for language processing and production, like pars-opercularis of the inferior frontal gyrus (BA44) and the middle frontal gyrus (BA46), which basically compose the Broca's area, and the inferior parietal lobe (BA40), mostly corresponding to Wernicke's region along with the supramarginal gyrus and a portion of middle temporal gyrus (Fig. 3A) (Binder et al., 1997; Cappa, 2012; Papathanassiou et al., 2000; Simos et al., 1999). Moreover, regions associated to memory processing (mid and inferior temporal lobe [BA21, BA20], middle frontal gyrus [BA46], posterior cingulate cortex [BA23]) have been also identified. Interestingly, regions being crucial for brain integrity in Low-IQ subjects were all, partially or completely, related to the manipulation of emotional content, more precisely left amygdala, right anterior cingulated cortex (ACC) and left temporal pole (Devinsky, Morrell, & Vogt, 1995; Jimura, Konishi, & Miyashita, 2009; Kobayashi, 2011; Morris et al., 1998) (Fig. 3B).

Given such language-related difference, the possibility of a gender-related effect was investigated, resulting in a null difference in the robustness level between female and male participants (Fig. 4A). Such finding promoted a further exploration of possible differences in the functional connectivity profile of these regions with respect to their correlation with intelligence and brain resilience to lesions. In the context of a generalized difference in the overall connectivity profile of High and Low IQ subjects (Fig. 4B), we consequently investigated for potential differences in the average regional connectivity of subjects with High and Low IQs by the means of seed-based pairwise connectivity analysis. The results of between-group comparisons ($p < .05$, FDR-corrected) for language network's nodes (additional regions' connectivity profiles are included in Figure S4) and emotion-related regions are reported in Figs. 4C and 5B respectively. Finally, in order to get an insight about the role of such regions in the overall brain organization at rest, we also looked at the connections between these regions and anatomically-defined RSN (Fox et al., 2005). Therefore, average seed-to-network functional connectivity values have been calculated in both groups, referring to well-known RSN encompassing the default-mode, fronto-parietal control, frontal attention, language, somatomotor, auditor, visual and working memory networks (Allen et al., 2011; Mantini et al., 2007). The results of group comparison (all $p < .05$, Bonferroni corrected) are presented in Fig. 4D (High > Low IQ) and Fig. 5A (Low > High IQ) as the average seed-to-network profile of subjects with High and Low-IQ. Despite region-specific variations in the differential connectivity patterns, an overall trend for a major involvement of the fronto-parietal control, frontal attention and working memory RSNs emerged in both groups. Additional details about the aforementioned statistical analyses are included as supplementary Material and Methods.

Finally, given the interesting link between CR and age (Bastin et al., 2012; Zihl, Fink, Pargent, Ziegler, & Buhner, 2014), we also looked at their potential interaction with intelligence.

Table 1 – Average values for Full scale (FSIQ), Performance (PIQ) and Verbal IQs (VIQ) both for the overall sample and for High and Low-IQ groups. Main effects of between group ANCOVA are reported (covariates of age and total brain volume), post-hoc comparisons were all significant ($p < .05$, Bonferroni corrected). Legend: BD = block design; VOC = vocabulary; SIM = similarities; MAT = visuo-spatial abstract reasoning matrices.

	Overall dataset		High IQ		Low IQ		ANOVA main effect	
	M_{102}	SD_{102}	M_{102}	SD_{102}	M_{102}	SD_{102}	*F*	*sig.*
FSIQ	114	11	119	7	84	5	156.234	<.001
VIQ	111	9	116	5	89	9	16.235	<.01
PIQ	109	11	121	6	86	6	94.213	<.001
BD	54	9	65	4	40	5	129.143	<.001
VOC	56	9	61	6	52	9	9.552	<.01
SIM	52	7	58	5	43	9	25.67	<.01
MAT	51	6	62	5	46	6	59.511	<.001

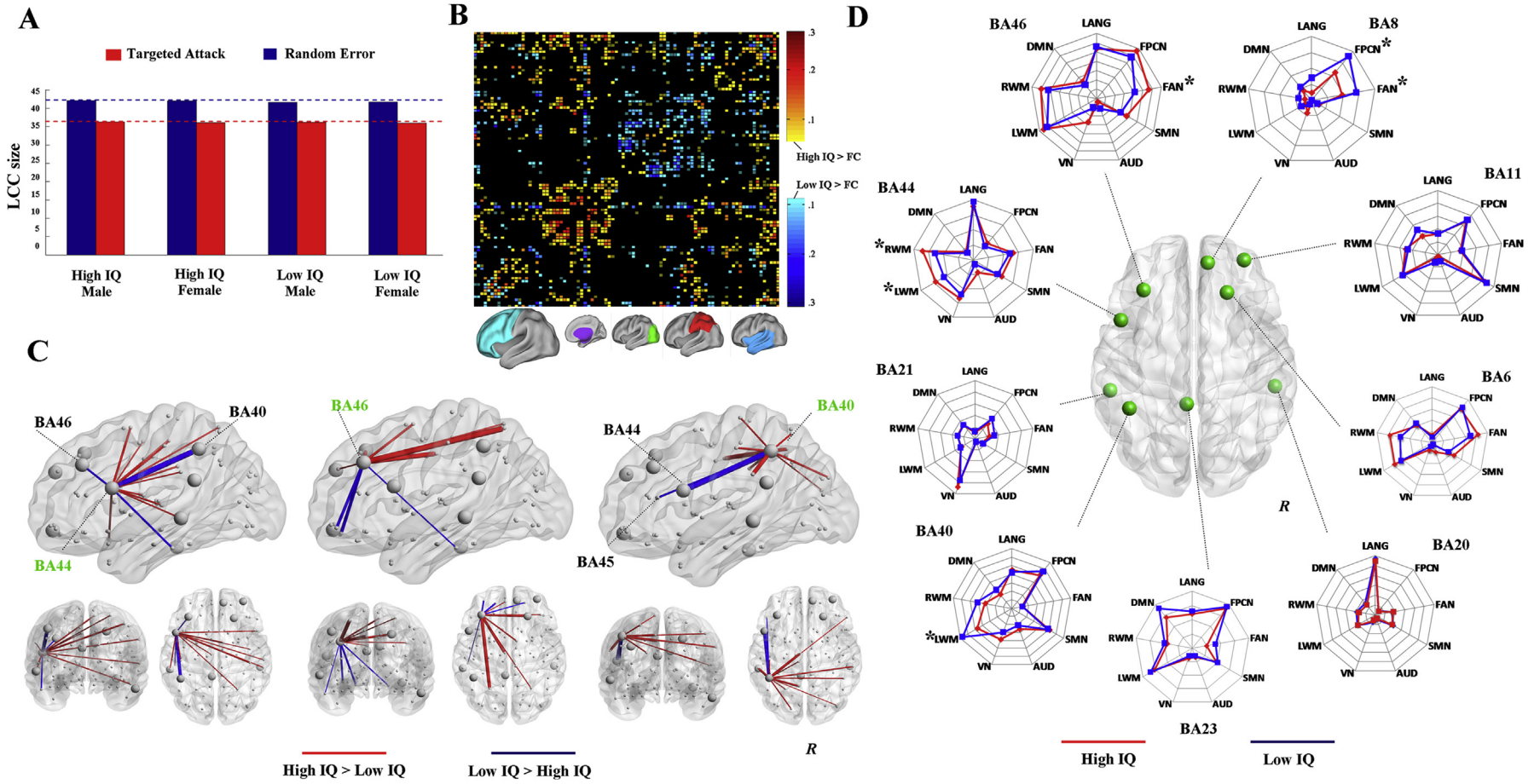

Fig. 4 – Pairwise functional connectivity and seed-to-network analysis results. Panel A shows no differences in the average size of the LCC in male and female participants, ruling out the hypothesis of a gender-effect as responsible for the major involvement of language-related regions (BA40, 44 and 46) into High and Low-IQ individuals discrimination, while a difference in the pairwise connectivity profile referring to frontal, limbic and parietal lobes emerged (B) (color code represent differences in functional connectivity – FC). A subsequent seed-based connectivity analysis based on those regions responsible for the largest drop in *LCC* size in High and Low-IQ participants has been performed, with the results for language-related regions reported in panel C. Interestingly, a pattern of decreased between-regions connectivity, as well an increased long-range, mostly inter-hemispheric connections for participants with higher IQ were identified (C, $p < .05$; results for remaining regions are included in Fig. S5). Moreover an additional connectivity analysis between the regions responsible for the largest LCC drop in High-IQ participants and anatomically-defined resting-state networks (RSN) has been tested: this, showed a region-specific pattern of group differences in connectivity, mostly involving left and right working memory (WM), frontal attention (FA) and fronto-parietal control (FPC) networks. *indicate statistically significant IQ-related differences in seed-to-RSN correlation coefficient ($p < .05$, Bonferroni corrected).

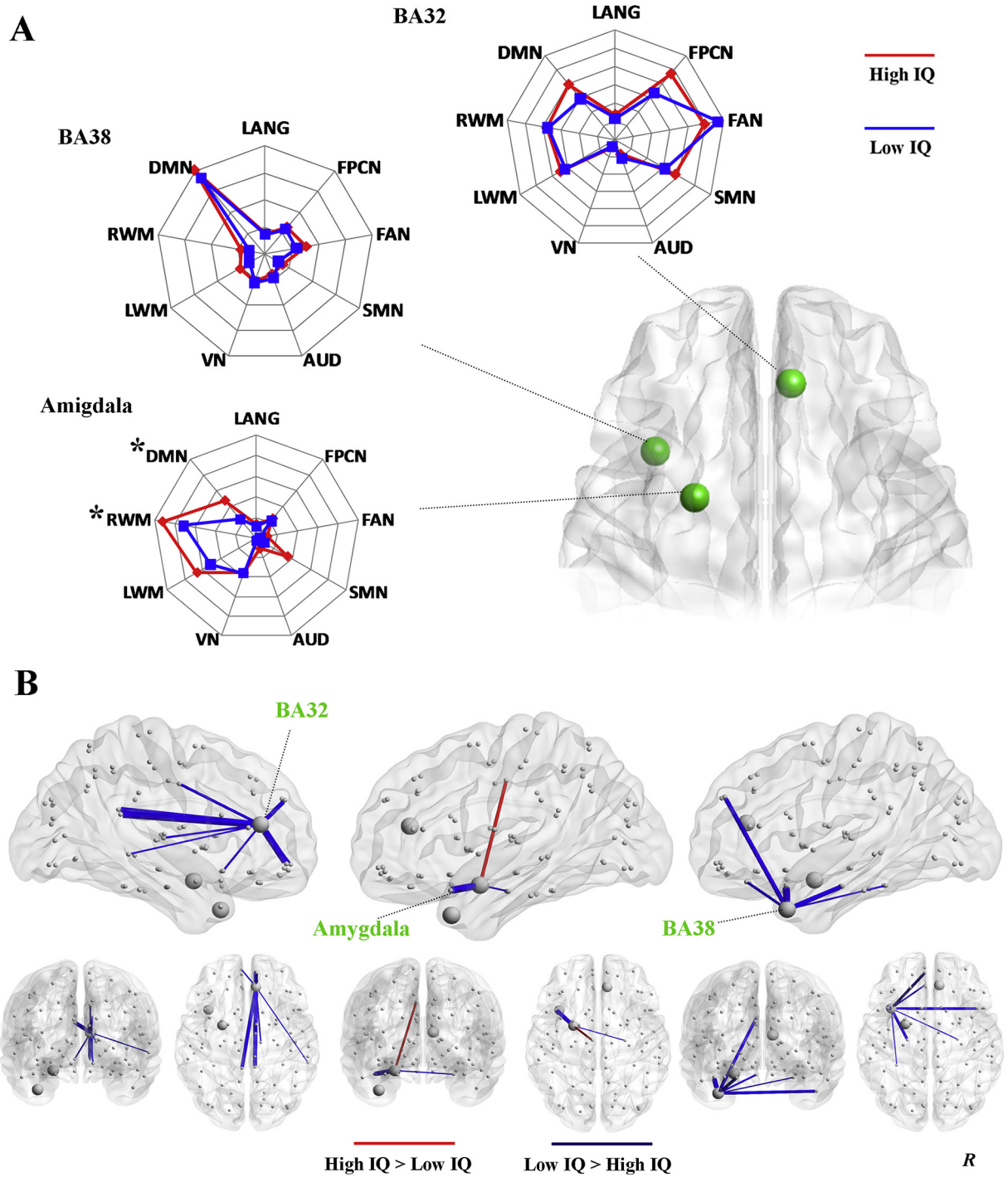

Fig. 5 – Functional connectivity analysis in regions responsible for greater LCC drop in Low-IQ participants. Panel A and B respectively show the results of seed-to-RSN and pairwise functional connectivity analyses for regions shown in Fig. 1B (i.e., left amygdala, left temporal pole and right anterior cingulate cortex – ACC). Increased connectivity in Low-IQ participants between amygdala and both DMN and right WM network were identified, as well as increased connectivity between left ACC and the Fronto Parietal Control Network (FPCN). *indicates statistically significant IQ-related differences in seed-to-RSN correlation coefficient ($p < .05$, Bonferroni corrected).

By contrasting a model including the average LCC values of High and Low-IQ subjects in different decades (see Supplemental Methods and Results), we identifying a trending to significance interaction between robustness, age and intelligence, possibly forced by an augmented robustness in High-IQ subjects older than 50 years respect to Low-IQ ones, with data related to TA being more coherent along the entire age range (Fig. S4).

4. Discussion

Recent advances in brain modeling and neuroimaging techniques have contributed to a better understanding of the neurobiological correlates of intelligence (Haier, Jung, Yeo, Head, & Alkire, 2004; Penke et al., 2012; Van Den Heuvel et al., 2009). Interestingly, the correlation between intelligence and epidemiological factors has been demonstrated as well, with higher IQ people being reported as having, for instance, a higher survival rate and a better social economic status (Deary, 2008; Gottfredson, 2004; Pierce, Miller, Arden, & Gottfredson, 2009). While intelligence level has been promoted as a mediator for more efficient behavior, like improved decision-making abilities in everyday life, no evidence has been reported for a more direct link between intelligence level and brain intrinsic properties related to its ability to cope with the loss of its functional units. Here we document a correlation between IQ and brain robustness as measured through resting-state fMRI graph-theoretical analysis, with specific subsets of cortical and subcortical regions mostly responsible for such brain feature. This suggests a possible link between the development of specific cognitive abilities, the consequential shaping of their neuroanatomical and neurophysiological substrates, and a resultant behavioral pattern inherently leading to improved robustness towards brain insults.

Robustness is a ubiquitously observed property of complex, evolvable systems (Kitano, 2004). Given its multidimensional nature, encompassing organic biology, mathematics, sociology and engineering, our finding allow for a series of theoretical and practical considerations. Therefore, we will summarize our discussion focusing on *(i)* the possible biological underpinnings of the intelligence-brain robustness interaction, *(ii)* its impact into determining individual robustness towards acute or chronic brain diseases, *(iii)* the investigation of the role of the specific regions responsible for the observed correlation and the meaning of the different interaction with TA and RE, as well *(iv)* the potential implications of these results concerning Non-Invasive Brain Stimulation (NiBS) techniques.

4.1. *Robustness and evolvability*

Looking at the evolutionary role of "robustness" for biological system, a correlation between intelligence and brain robustness to damage sounds like an oversimplified yet expected finding. While conceptualized within the framework of different self-organization models, like the "Highly Optimized Tolerance" (HOT) (Carlson & Doyle, 1999), the scale-free network by preferential attachment (Barabasi & Albert, 1999) and the self-organized criticality ones (Bak & Paczuski, 1995), robustness is generally defined as the main feature that allows a system to maintain its functions in case of external and internal perturbations (Kitano, 2004). It indeed represents a clear example of those fundamental systems-level phenomena, self-emerging from the inherent structure of the system itself and impossible to be fully understood by looking at the individual components of the network. Interestingly, from the biological point of view, robustness usually shares the same architectural requirements of evolvability, giving reason why it is ubiquitously reported in living organisms that have evolved (Kitano, 2004). More generally, two central features of complex systems' architecture have been proposed as able to facilitate evolvability and robustness: a highly resilient and conserved core of processes working as an interface for diverse inputs and outputs (signaling, nutrients and products at the molecular biology level), and a more versatile mechanism, known as "weak linkage", that somehow sustains and facilitate the proper exchange of information between different units of the main core (De Visser et al., 2003; Kirschner & Gerhart, 1998). Interestingly, the human brain is considered among the most complex system in nature, with some of its structural features strongly resembling network behaviors ascribed to other biological systems, for instance small-world configuration (Achard & Bullmore, 2007; Downes et al., 2012). Furthermore, the very idea of a stable "central core" has been recently translated at the brain level as well, with a "functional backbone" documented as the main component of resting and evoked activity in human and other mammals brains (Van Den Heuvel, Kahn, Goni, & Sporns, 2012; Van Den Heuvel & Sporns, 2013). As a complementary finding, in a previous study we have documented how the vast majority of intelligence-related individual differences in functional connectivity falls in the spectrum of the so called "weak ties", i.e., weak connectivities within the left tail of the distribution (Santarnecchi, Galli, Polizzotto, Rossi, & Rossi, 2014), a finding which has been confirmed also in the current study (see Fig. S2). This similarity posits the suggestive idea that, like for robustness and evolvability, also intelligence might be considered a "dominant" phenotype whose biological implications are observable in terms of a better ability to cope with unexpected events.

4.2. *Robustness and brain pathology*

In fact, our results sustain the idea of intelligence as able to explain part of the individual differences in the robustness towards neurodegenerative or suddenly intercurring pathological conditions, suggesting a possible connection with the CR model (Stern, 2009). The idea that "some people appears to be more resilient to brain changes than others" (Stern, 2012) has opened a new research field in contemporary neuroscience, aimed at understanding both the underlying mechanisms and candidate biomarkers for this buffer, with evidences also pointing at specific brain topology configurations which have been proven to be altered in pathological conditions. Interestingly, even though brain robustness has not been tested in a large number of pathological conditions, alterations in network metrics highly correlated with robustness, such as clustering coefficient, modularity and small-worldness, have been reported in schizophrenia (Bassett et al., 2008; He et al., 2012; Yu et al., 2011), Alzheimer's disease (Reijmer et al., 2013; Zhao et al., 2012), autism (Belmonte et al., 2004; Maximo, Keown, Nair, & Muller, 2013), ADHD (Castellanos, Kelly, & Milham, 2009; Castellanos & Proal, 2012), and dementia (Pievani, De, Wu, Seeley, & Frisoni, 2011). Furthermore, our finding suggest topological properties among those related to distributed information processing – instead of local computation-as mostly representative to the

robustness–intelligence correlation, suggesting a potential framework for the ability to successfully reallocate resources behind the CR model. Interestingly, the idea of a possible correlation between premorbid brain robustness level and individual shielding towards pathology also seems to couple together with recent contributions documenting how intelligence level effectively shapes brain networks dynamics towards a pattern strongly supporting the CR concept (Fischer, Wolf, Scheurich, & Fellgiebel, 2014; Stern, 2009). While our data provide new interesting insights in this direction, also promoting a possible age-dependent modulation of such interaction as well as partially excluding potential interaction with "brain reserve" (Bartres-Faz & Arenaza-Urquijo, 2011; Stern, 2002), longitudinal studies involving both healthy and pathological subjects across the life span are needed.

4.3. *The intelligence–robustness interaction in the brain*

The differential interaction between intelligence level and the robustness to TA and RE might reflect the network-structure idea behind these two diverse – basically opposite-types of robustness indexes. While the former process is based on targeting the most important region(s) of the brain first, thus theoretically inducing the larger disruption to the overall network integrity in just a few steps, the latter is based on a completely random targeting (Alstott et al., 2009), leading to different network organizations which may be better shielded against one or the other procedure. Given a highly centralized system where the vast majority of the information is handled by a small subset of network nodes – like the human brain, TA certainly represents the most dangerous configuration: stroke is a paradigmatic example, in which also its sudden occurrence might play a role in overall network dysfunction. On the other hand, the RE approach relies on the small probability that the most important regions (being just a small portion of the entire population) are being randomly targeted, making this procedure less likely to induce a dramatic network impairment, unless the lesioning process is protracted in time as in a slowly progressing neurodegenerative disease. The fact that intelligence, and more significantly FSIQ and VIQ, correlates mostly with robustness to TA inherently suggests how intelligence may interact – "shape" – brain network configuration. By implying intelligence as responsible for a more widespread and efficient brain resource allocation at rest, our results support previous observations of a positive spatial correlation between intelligence level and brain volumes -mostly encompassing frontal, parietal and occipital lobes (Colom, Jung, & Haier, 2006; Colom, Karama, Jung, & Haier, 2010), contrasting the idea of prefrontal cortices as primary brain sites related to intelligence level (Duncan et al., 2000). Moreover, in the context of the CR theory, this may give reason of the better capacity to keep the network working properly on the ground a less-centralized system, where different operations may be successfully executed along different paths. However, even though this implies an increased equality across brain regions importance, a small subset of regions still could play a predominant role in more intelligent brains, leading to two interesting findings.

First of all, identified regions encompassing frontal, parietal and temporal lobes resemble those belonging to a widely recognized theory about the neuroanatomical substrate of human intelligence, that is the Parieto-Frontal Integration Theory (P-FIT) (Jung & Haier, 2007) (see Fig. 6). In the last few

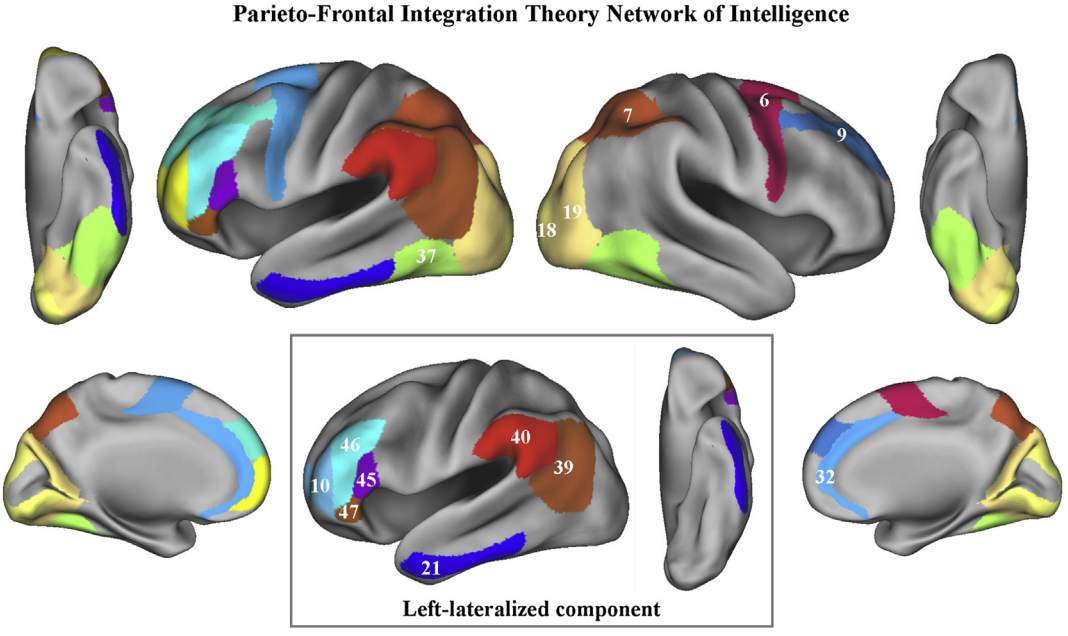

Fig. 6 – The P-FIT network of human intelligence. The most relevant brain regions (Brodmann areas) belonging to the Parieto-Frontal Integration Theory network are plotted on an inflated brain surface. The figure shows both the overall bilateral network and a subsample composed solely by those regions being present uniquely on the left hemisphere (left-lateralized component) and highly resembling the network identify in High-IQ individuals. Numbers represent Brodmann areas.

years the P-FIT has received large experimental support using a number of imaging techniques, such as structural (Narr et al., 2007), diffusion weighted (Chiang et al., 2009) and functional MRI (Choi et al., 2008; Yuan et al., 2012), circumscribing the individual variability in intelligence level to the functional coupling between prefrontal, parietal and temporal lobes regions interplay. It is therefore reasonable that the same regions also contributed to the overall intelligence-related increase in network robustness, which is in turn dependent on their centrality and global efficiency (Alstott et al., 2009). Generally, our results confirm the idea of a primary role of parietal, frontal and temporal regions into explaining intelligence variability, meanwhile originally suggesting these very regions as also responsible for higher brain robustness in more intelligent subjects. However, whether the increase in intelligence level do trigger or, on the contrary, results from the inherent modulation of brain networks organization -which in turn lead to an increase in robustness- remains obscure. Such hypothesis would require a longitudinal evaluation or larger cross-sectional studies in order to look at the interaction between these factors at different ages. Secondly, the subset of regions showing the higher discriminatory power between High and Low IQ subjects are integral part of the language processing network, specifically the pars-opercularis of the inferior frontal gyrus (BA44), the inferior parietal lobe (BA40) and the middle frontal gyrus (BA46) (Binder et al., 1997; Simos et al., 1999). Interestingly, an additional seed-based functional connectivity analysis on these language-related regions showed a peculiar difference in the functional connectivity profile of the two IQ classes, with High-IQ individuals reporting decreased within-network and increased network-rest-of-the-brain connectivity with respect to Low-IQ ones. Moreover, these regions also showed, for instance, significantly increased and decreased connectivity between working memory RSNs and, respectively, prefrontal and parietal regions. The interpretation of these results clearly goes beyond the intent of the present study, even though they suggest how those regions responsible for the drop in the *LCC* size may represent a core set of brain areas whose connectivity might play a role to explain IQ-related individual differences, regardless of their role for robustness. Further studies are required to explore such interaction by adopting a more in-depth battery of neuropsychological tests specifically focused on these cognitive dimensions. Moreover, fluid (*Gf*, represented here as PIQ) and crystallized (*Gc*, represented here as VIQ) components of intelligence did not show any significant differential interaction with brain robustness to TA. Even though verbal and performance WASI subscores can be roughly utilized as estimates of *Gf* and *Gc*, such distinction is not entirely part of the theoretical work behind nor the WASI (Weschler, 1999) neither its full-length counterpart WAIS (Weschler, 1997). Therefore, such hypothesis should be then tested using specifically tuned instruments as well (Matzen et al., 2010; Santarnecchi et al., 2013).

4.4. *Robustness as a testing platform for brain flexibility*

Finally, it is noteworthy that the theoretical approach described here cannot take into account that a TA may trigger adaptive mechanisms in the living brain (i.e., brain plasticity), which usually tends to partly compensate the effects of the lesion. However, this opens new interesting scenarios where the predictive power of this kind of simulation over the actual recovery observed in patients may be tested. For instance, increasing spatial resolution of the TA may lead to the identification of fine-grained robustness-based biomarker, which may be applied in early stages of neurodegenerative processes. Moreover, the interaction between intelligence and brain resilience could also be tested in a dynamic fashion using agent-based models (Joyce, Hayaska, & Laurienti, 2012; Joyce, Laurienti, & Hayasaka, 2012), where the reaction of the network to the injection of a signal in a specific node is tested through time (Joyce, Hayasaka, & Laurienti, 2013). Within the same context, current results also open an original perspective into the understanding of the mechanisms by which brain stimulation techniques as Transcranial Magnetic Stimulation (TMS) (Barker, Jalinous, & Freeston, 1985; Pascual-Leone, Walsh, & Rothwell, 2000; Rossi & Rossini, 2004), transcranial Direct Current Stimulation (tDCS) or transcranial Alternate Current Stimulation (tACS) (Nitsche & Paulus, 2011; Paulus, 2011) might exert their actions on brain networks by physically inducing the targeted (or random) attacks we have modeled. The field of "perturbation-based imaging" is exponentially growing, both for research and clinical perspectives (Pascual-Leone et al., 2011; Rossini & Rossi, 2007), based on the concept that these techniques, at experimenters' demands, can allow to both inhibit (i.e., "disconnect" from the system, a process which resemble our node-depletion approach) or even enhance specific brain regions activity (Feurra et al., 2011; Rossi & Rossini, 2004; Santarnecchi et al., 2013; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008), with a cascade of effects over nodes belonging to the same network or even in remotely interconnected regions (Casali, Casarotto, Rosanova, Mariotti, & Massimini, 2010; Massimini, Boly, Casali, Rosanova, & Tononi, 2009; Polania, Paulus, Antal, & Nitsche, 2011). To correlate connectivity patterns obtained using TMS-EEG or TMS-fMRI in individual with different cognitive profiles could provide insights about the relationship between brain response (in a sense, an index of "brain flexibility", which might partly account for individual responsiveness to the external perturbation) and general cognitive features, thus confirming the protective role of higher order cognitive functions.

5. Conclusion

Current results contribute to widen the concept of intelligence from "the substrate required to solve complex tasks" towards a factor significantly influencing several aspects of human well-being through behavioral and biological cascade effects, also promoting the evolutionary role of higher order cognition and its protective role against aging and neurodegenerative process.

Authors' contributions

E.S. designed research; E.S. analyzed data; E.S. and S.R. critically interpreted results and wrote the paper, S.R. and A.R. supervised the study.

Financial disclosures

All authors report no conflict of interest.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2014.11.005.

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