The impact of aging on human brain network target controllability

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Abstract
Understanding how few distributed areas can steer large-scale brain activity is a fundamental question that has practical implications, which range from inducing specific patterns of behavior to counteracting disease. Recent endeavors based on network controllability provided fresh insights into the potential ability of single regions to influence whole brain dynamics through the underlying structural connectome. However, controlling the entire brain activity is often unfeasible and might not always be necessary. The question whether single areas can control specific target subsystems remains crucial, albeit still poorly explored. Furthermore, the structure of the brain network exhibits progressive changes across the lifespan, but little is known about the possible consequences in the controllability properties. To address these questions, we adopted a novel target controllability approach that quantifies the centrality of brain nodes in controlling specific target anatomo-functional systems. We then studied such target control centrality in human connectomes obtained from healthy individuals aged from 5 to 85. Main results showed that the sensorimotor system has a high influencing capacity, but it is difficult for other areas to influence it. Furthermore, we reported that target control centrality varies with age and that temporal-parietal regions, whose cortical thinning is crucial in dementia-related diseases, exhibit lower values in older people. By simulating targeted attacks, such as those occurring in focal stroke, we showed that the ipsilesional hemisphere is the most affected one regardless of the damaged area. Notably, such degradation in target control centrality was more evident in younger people, thus supporting early-vulnerability hypotheses after stroke.

Keywords Aging · Network controllability · Brain connectivity · Stroke · Simulation · MRI

Introduction
Brain controllability refers to the possibility to induce specific functional states, or configurations, by means of internal or external control. In neuroscience, this capability is associated with cognitive control (Botvinick and Braver 2015), which can be qualitatively assessed by measuring dynamic cooperation and competition between different neural systems during goal-directed tasks (Cocchi et al. 2013). Recently, the adoption of a control theoretic perspective has started to provide quantitative insights on how functional brain states can be predicted by the underlying brain network structure (Gu et al. 2015). In particular, network controllability—i.e., the theoretical ability to guide a system’s state by operating on few driver nodes—has received a growing interest in several biological applications (Yan et al. 2017; Ravindran et al. 2017, 2019; Vinayagam et al. 2016). Controllability of brain networks has been specifically explored to understand how the brain is able to endogenously modify its dynamics and if it is possible to steer it from exogenous stimuli (Tang and Bassett 2018; Muldoon et al. 2016). Hence, a crucial step in network controllability is to determine the nodes that are the best suited to drive the system’s state. To this end, centrality measures based on controllability were developed and applied to brain networks for identifying potential driver nodes and measuring the size of the network that they can control (Gu et al. 2015; Pasqualetti et al. 2014). These studies can have practical implications because they can inform possible intervention strategies to favor specific patterns of behavior or treat brain diseases, by means of brain stimulation technology (Bikson et al. 2016; Wilson and Moe-Hilis 2015; Tang and Bassett 2018).
While promising, controllability of the brain is still an underexplored research field due to the different ways in which controllability can be implemented (Jiang and Lai 2019). In practice, controlling the whole system from a single node could not be feasible due to algorithmic imprecision even in relatively small networks of hundreds of nodes. Furthermore, the magnitude of the control signal might be too high to be generated physically or destructive for the network functioning itself (Suweis et al. 2019; Tu et al. 2018). A possible solution would be to focus on specific parts of the network so as to reduce the overall computational complexity (Yan et al. 2017; Gao et al. 2014; Chen and Yong 2020). Determining how single nodes can affect parts of the network still remains poorly understood in the human brain. Furthermore, current results have neglected the fact that brain controllability could vary with aging, which induces progressive changes in the underlying network structure or with focal brain damages (Zhao et al. 2015; Gong et al. 2009).

To address these questions, we used cross-sectional anatomical DTI and functional MRI (fMRI) data from 171 healthy individuals aged between 5 and 85 (Brown and Van Horn 2016). Then, we evaluated the ability of single brain nodes to control specific target subsystems, i.e., frontal, limbic, temporal, sensorimotor, parietal, and occipital systems (Fig. S1). To do so, we adopted an exact network controllability approach (Bassignana et al. 2021), which gives for each tested driver the number of nodes in a predetermined target that it can control (Fig. 1).

We then studied how control centrality is distributed in the brain and which are the most controllable target systems. We assessed how control centrality is altered by age and whether there are specific regions that better explain the aging process. Finally, we tested how control centrality changes in presence of simulated targeted attacks and how the overall damage depends on the participant’s age.

**Results**

**Sensorimotor areas have high control centrality**

We first studied how target control centrality is distributed across different functional systems of the human brain (Fig. 2, Methods). Namely, we analyzed the ability of a single node in controlling different cortical systems by computing the target control centrality $\tau$, the number of target nodes that this driver can control (Methods). The group-averaged results showed that $\tau$ values significantly vary across regions (one-way ANOVA, $df = 5, F > 969, p < 10^{-6}$) as well as depending on the targeted system. In particular, the sensorimotor regions had a high tendency to control the nodes in other systems, but they were also difficult to control from other areas (Fig. S2). By pooling the results obtained with all different target systems, it became clearer that the sensorimotor nodes have on average the largest centrality values, while the limbic nodes have the lowest ones (Fig. 2a).

Next, we evaluated the tendency of single brain areas to control the system they belong to as compared to other systems. To this end, we calculated the self-regulation score of a node as the ratio of $\tau$ when targeting its own system and the average obtained when it targets all the other systems (Methods). Results showed that on average brain regions tend to have a high self-regulation so that they control more nodes in their own system than those in other systems (one-way ANOVA, $df = 4, F > 1405, p < 10^{-6}$). That was particularly true for the sensorimotor system which consistently presented the highest values of the self-regulation score. On the contrary, the nodes in the limbic system exhibited a very low self-regulation (Fig. 2b).

![Fig. 1 Illustrating principle of the step-wise target control centrality. Left panel: the lower triangle indicates the selected driver node, upper triangles indicate the nodes in the chosen target system. The structural brain network derived from DTI data is the connection matrix of the LTI control system. Right panel: the step-wise algorithm identifies the controllable driver-target configuration by visiting the target nodes according to their strength in the fMRI functional network, i.e. from the highest to the lowest](image-url)
Control centrality decreases with age

By exploiting the high variability in the age of the participants (mean 35.8 years, std 20.0 years), we asked whether and how target control centrality varied with age. To this end, we computed the Spearman partial correlation between the $r$ values and age of the participants, correcting for the outdegree of the nodes. This correction was needed to exclude the existence of significant associations merely due to the presence of nodes with a high number of outgoing links. Results show a general tendency of the brain areas to be negatively correlated ($r_{\text{var}} > 0.15$, $p < 0.05$, FDR-corrected for multiple comparisons) with age regardless of the targeted system (Fig. S3). The presence of positive correlations is instead less consistent and weakly concentrated in the frontal and central areas of the brain.

By focusing on the ROIs that presented a significant association with the same sign across all targets, four regions emerged with a consistent negative correlation with age (Fig. 3). Among those, the right lateral occipital inferior area (RLOCid3) in the occipital system is known to be associated with attentional processes and related to the dorsal attention network (Zhang et al. 2019). The other regions were in the temporal system and three of them (left middle temporal anterior gyrus (LMTGad), left middle temporal temporo-occipital gyrus (LMTGtp), right middle temporal posterior gyrus (RMTGpd)) belonged to the default mode network (DMN) (Xu et al. 2016; Davey et al. 2016). The left middle temporal temporo-occipital gyrus (LMTGtp) had the strongest negative correlation, possibly related to hippocampal degeneration with age (Scheltens et al. 1992) (Fig. 3a). Taken together, these results suggested that most brain regions, and in particular those located in the temporal system, tend to decline with age.

Targeted attacks lead to greater control centrality loss in younger brains

Finally, we asked to what extent the target control centrality was impacted by attacks to specific brain systems, like those occurring after stroke, traumatic brain injury or tumor resection (Charras et al. 2015; Salvalaggio et al. 2020). To answer this question, we simulated lesions to different target systems by removing the nodes and the links from only one hemisphere. Then, we evaluated the ability of all the other nodes to control the contralesional part of the target in the intact hemisphere, and we computed the difference with the original values ($\Delta_{\text{attack}} = r_{\text{lesion}} - r$) to quantify the impact of the damage.

As expected, network attacks led to decreases of control centrality, with greater losses in the ipsilesional hemisphere as compared to the unaffected one (two-way
ANOVA, $df = 4, F > 15, p < 10^{-6}$, Figs. 4, S4). In particular, results showed that control centrality losses $\Delta_{\text{attack}}$ were globally small when the sensorimotor system was lesioned. Instead, when other systems were damaged, the sensorimotor system exhibited larger $\Delta_{\text{attack}}$ decrements. Conversely, the limbic system was relatively mildly impacted by any attack. In terms of difference between hemispheres we did not report a clear pattern across damaged systems. However, we consistently observed a greater ipsilesional centrality loss when the parietal system was attacked on the right hemisphere (two-ways ANOVA, $df = 4, F > 204, p < 10^{-6}$, Fig. 5), which would reflect the ability of the right parietal lobe to be involved in several high order cognitive processes (Corbetta et al. 2008; Husain and Nachev 2007; Bartolomeo and Seidel 2019) and interacting more with the other hemisphere as compared to the left one (Gotts et al. 2013; Koch et al. 2011).

Finally, we evaluated whether the age of the participants had an impact on the observed node control centrality loss after the simulated network attacks. Results showed a global positive correlation between $\Delta_{\text{attack}}$ values and age (Spearman correlation, $|R| > 0.15, p < 0.05$, FDR-corrected for multiple comparisons), Figs. 6, S5), suggesting a more important effect in younger participants compared to adults. Notably, these associations were consistently reported in the same temporal DMN areas, for which we also observed a significant positive correlation between control centrality values and age (Fig. 3).

**Discussion**

**Driver nodes in the human brain**

Thanks to its ability to establish theoretical relationship between structure and dynamics, control network theory has been increasingly adopted to study human brain functioning. Control centrality, measuring how important a network node is in influencing other nodes’ states, has been shown to provide useful markers of brain dynamics during resting states (Gu et al. 2015) and executive functioning (Cui et al. 2020), as well as to predict responses to brain stimulation in practice (Medaglia et al. 2018) and in theory (Muldoon et al. 2020). These findings establish an intuitive link between the brain regions identified as potential control drivers and the current knowledge in cognitive neuroscience. Notably, large-scale brain activity has been found deeply dependent on nodal controllability within specific systems, such as default mode, fronto-parietal, cingulo-opercular, and attention (Honey et al. 2010).

While these results provide mechanistic insights on how single areas can steer whole-brain activity, they do not inform on how different specialized brain systems can
influence each other. Is there a dominant subnetwork prone to control all the other ones? Is there a subsystem that is instead more controllable than others? These fundamental questions become particularly pressing considering that one-to-whole control might be difficult to achieve both from a theoretical and practical angle (Suweis et al. 2019; Tu et al. 2018). To answer those questions, we used the step-wise target control centrality, i.e. an optimized Kalman-based heuristics that measures the ability of nodes to control predetermined target parts of the network (Bassignana et al. 2021).

**Fig. 4** Loss of target control centrality after simulated attacks. Panel a shows the cortical maps of the group-averaged $\Delta_{attack}$ values when attacking different target systems on the left hemisphere (see Fig. S4 for attacks to the right hemisphere). Size and color of the nodes are proportional to the decrease of target control centrality with respect to the healthy situation. Panel b shows the values of the $\Delta_{attack}$ averaged across the nodes of a same system. Both values for the systems in the ipsilesional and contralesional hemisphere are illustrated. Error bars stand for the standard error across participants.

**Fig. 5** Comparison of target control centrality loss between lesions to the right and left parietal system. Left side panel illustrates the group-averaged values for the $\Delta_{attack}$ of the intact systems when attacking the ipsilateral parietal system. Error bars stand for the standard error across participants. Right panels show the cortical maps of the group-averaged $\Delta_{attack}$ values when attacking respectively the parietal system in the left (L) and right (R) hemisphere.
Our results showed that in general node control centrality varies depending on the targeted system. Despite such variability, the sensorimotor areas always exhibited the highest influencing capacity while being very hard to control. Conversely, the limbic regions always had a scarce driving power and they were on average easily controllable by all other nodes (Fig. 2). This tendency was also confirmed when looking at the ability of those systems to control, or self-regulate, themselves.

The sensorimotor system is known to be more densely connected, with many anatomical long-distance interhemispheric connections, as compared to other secondary motor-related systems (Narayanan et al. 2005). Such hyperconnectivity, would constitute, therefore, a structural prerequisite to reach and orchestrate different areas during cognitive and motor functions (Paquola et al. 2019; Shañeí et al. 2020; Wang 2020; Vázquez-Rodríguez et al. 2019; Demirtaş et al. 2019). From a functional perspective the high control centrality of the sensorimotor system has been previously associated with its ability to process information not only for motor control but also for a broad range of recognition processes (Sohn et al. 2021; Bassett et al. 2015; Adolphs et al. 2000). This is in line with the existence of gradients of cortical organization through which the sensorimotor system could boost neural activity of other association areas required for higher order functions such as cognitive control, guided attention and motivation (Kong et al. 2021). In line with such a cortical organization gradient, we could have expected that the visual system—another highly connected primary system—would have exhibited high control centrality, too. However, the control centrality of the nodes in the occipital lobe, where main hubs of the visual system are localized, were rather low. Future works will be crucial to assess whether the high control centrality of the sensorimotor system is mainly due to its high connection density and/or specific local synaptic properties and gradients of gene expression in the excitation-inhibition balance of related interneurons (Kong et al. 2021).

While limbic areas constitute an important structural bridge for the information transfer between cortical and subcortical regions (Rolls 2015; Catani et al. 2013), their control centrality was remarkably low regardless of the targeted cortical system. This could be in part explained by the heterogenous nature the limbic system, which includes different anatomical and cytoarchitectonic components (Catani et al. 2013; Kaas 1995; Rasia-Filho et al. 2021). However, it is also true that many important subcortical areas, such as amygdala, caudate nucleus, and hypothalamus (Rolls 2015), were not available in the dataset we used (see “Methodological considerations” for more details). Future research will be
crucial to elucidate the role of limbic areas in terms of target control centrality using more comprehensive and accurate subcortical-cortical systems.

**Aging and control centrality**

Brain aging is a highly heterogeneous and dynamic process that involves structural and functional changes both at individual and group level. Among structural changes, cortical thinning and regional atrophy (Bakkour et al. 2013), white matter loss of integrity (Damoiseaux et al. 2009), neuronal loss and degeneration (Allen et al. 2005) and neurotransmitters depletion have been detected at varying degrees among older subjects (Allen et al. 2005). Functional alterations refers to maladaptive, age-related brain activity, detected in neuroimaging studies, including decreased specificity of ventral-visual and motor areas (Bernard and Seidler 2012; Voss et al. 2008), decreased memory-related recruitment of medial temporal lobe regions (Cabeza et al. 2004) and dysregulation of the default mode network (Park and Reuter-Lorenz 2009).

Network approaches investigating brain reorganization across the lifespan have constantly reported whole-brain intrinsic connectivity changes by using standard centrality metrics such as node degree (Hampson et al. 2012), strength (Bagarinao et al. 2020) and betweenness (Bagarinao et al. 2019). Compared to young adults, older ones exhibit reduced local-efficiency and modularity as well as connectivity changes within and between specific subnetworks (Geerligs et al. 2015; Betzel et al. 2014; Song et al. 2014; Spreng et al. 2016). Only few studies have attempted to study how network controllability evolves with age. In a recent study, authors showed that regional controllability increases with development (Tang et al. 2017), but no information is available on how it evolves across the lifespan. To address this question, we combined information from both structural (DTI) and functional (FMRI) neuroimaging data, and we analyzed the effect of aging on a new measure of centrality based on network controllability.

Main results showed that control centrality was negatively correlated with age indicating a global trend of node controllability reduction in older brains. The presence of sporadic positive correlations in the frontal and central areas should be further investigated for possible compensatory mechanisms occurring in later age as well as in mild cognitive impairment and Alzheimer’s disease (Kubicki et al. 2016; Behfar et al. 2020; Guillon et al. 2019). Instead, brain regions in the middle temporal gyrus (MTG) were significantly impacted by aging, in terms of relative loss of control centrality (Fig. 3). Those areas were previously found to be less activated in elderly people, reflecting a lower semantic retrieval control process (Davey et al. 2016; Hoffman and Morcom 2018). Such a decrement could be associated with the the more general age-dependent DMN functional rearrangement (Grady et al. 2016; Li and Rieckmann 2014).

According to the “network dedifferentiation” hypothesis (Chan et al. 2014), DMN regions in older adults progressively present a reduction in the communication with other systems, such as the dorsal attention network (DAN) or the frontoparietal network (Spreng et al. 2016; de Schotten et al. 2005). Thus, age-related reduced control centrality could be a possible reorganizational mechanism subserving the failure to deactivate neural systems that are unrelated to the task (Grady 2012) and leading to abnormal increased brain activation (Duda et al. 2019; Morcom and Johnson 2015) and negative correlation with task performance (Buckner et al. 2008; Logan et al. 2002).

Our results showed that while there is a common distribution between the age-centrality correlations in the left and right hemisphere, there are also few notable differences. The specific asymmetric involvement of the right lateral occipital inferior cortex (ROLocid3) could be intriguingly related to a progressive inability to mediate the interaction between the right ventral attention system, involved in saliency analysis, and the bilateral dorsal attention system, mostly involved in attention shifting (Corbetta and Shulman 2002; Shulman et al. 2010; Bartolomeo and Seidel 2019). The interaction between the two attentional systems finally influences the processing of attended visual stimuli in the primary visual cortex (Murray and Wojciulik 2004; de Schotten et al. 2005). While asymmetry patterns could be interpreted in the light of age dependent loss of lateralization in specific cognitive processes, such as semantic control (Grady 2012; Cabeza 2002), more investigation is needed to better disentangle this aspect.

Finally, recent studies suggest that long-range connections may be more vulnerable to aging effects than short-range connections in both DMN and DAN (Tomasi and Volkow 2012). A future perspective would be to check to what extent the observed controllability changes depend on the relative spatial distance between the driver and target nodes.

Overall, our results indicated that age-related reduction in controllability in specific nodes at the crossroad of different brain systems relevant for cognitive control efficiency, could be viewed as a yet another evidence of a functional “reshaping” of brain networks along the lifespan (Spreng and Turner 2019; Grady 2012).

**Control centrality markers of brain lesions**

Network control theory not only informs on the basic brain functioning but it can also offer new analytical ways for quantifying dysfunctions in neurological diseases (Medaglia et al. 2017). After a focal damage, such as in stroke, traumatic injuries and tumors, the brain typically loses the
functions associated with the lesioned area and with those
connected to it. Quantifying the effects of such local destruction
on the rest of the network is, therefore, crucial to predict the extent to which the brain will recover its functions through a reorganizational process, i.e. plasticity (Cheng et al. 2012; Zhu et al. 2017).

Here, we studied how control centrality changed when simulating unilateral attacks to the target systems. Results showed that the nodes in the ipsilesional hemisphere globally underwent larger losses in control centrality. That was particularly true for the sensorimotor regions regardless of the system attacked. From a mechanistic perspective, the ability of the nodes in the damaged hemisphere to control the unaffected side of the target, would be compromised by the removal of the interhemispheric homotopic connections, i.e. the links bridging the homologous regions in the two hemispheres (Mancuso et al. 2019; Tang et al. 2016). The interruption of such homotopic bridge, which is typically stronger compared to heterotopic connectivity, eventually made the nodes in the intact target less reachable from the nodes in the lesioned hemisphere. The extent to which this also affects possible compensatory actions from the contralesional “intact” hemisphere, remains a question to be elucidated with more clinical and longitudinal data (Grefkes and Fink 2014; Buetefisch 2015; Bartolomeo and de Schotten 2016; Bartolomeo 2021; Kullmann 2019).

While the controllability power of ipsilesional sensorimotor regions was particularly impacted when damaging the targets, the other regions appeared to be less affected when the sensorimotor target was attacked. This weak effect was in part due to the relatively low values of control centrality of those regions, which limited the possible range of change after the damage. More generally, this might be related to a putative high reachability of the sensorimotor system given its high connection density (Reich et al. 2001; Narayanan et al. 2005; So et al. 2012) and the presence of alternative pathways between frontal, parietal and limbic areas (Griffis et al. 2019; Betzel et al. 2016).

We observed a progressive decrease of control centrality with age, mostly localized in the temporal lobes (Fig. 6). We then asked whether the control centrality losses induced by the lesions, regardless of the targeted system, could also depend on the age of individuals. Results confirmed that the damage-related control centrality reductions in the temporal lobes were larger in younger brains, which have in general higher baseline values of controllability.

From a biological perspective, it is well established that changes in neuroplasticity occur lifelong through many age-specific processes (Dosenbach et al. 2010), ultimately affecting cerebral network maturation (Fair et al. 2009; Supekar and Menon 2012) and controllability (Tang et al. 2017). Likewise, brain lesions could impact brain organizational properties in an age-dependent manner. In this direction, two seemingly contradictory explanations have emerged: first, “early plasticity”, arguing for the greater flexibility of the immature brain, and associated good recovery and outcome (Giza and Prins 2006; Kornfeld et al. 2015); and second, “early vulnerability” referring to the young brain’s unique susceptibility and subsequent poor outcome (Anderson et al. 2011; Max et al. 2010; Dennis et al. 2013).

Our results indicated that target control centrality follows an age-dependent trend that mirrors an early vulnerability condition, so that networks of younger participants are more impacted by focal lesions, possibly reflecting a reduced resiliency to damages in the early stages. Shedding a light on functional reorganization and recovery after brain injuries or stroke might enable better prediction and prevention of clinical outcome. However, the lack of clinical data for our population allows us neither to validate this result from a clinical perspective nor to assess the early-plasticity hypothesis which would require longitudinal clinical data associated with the recovery of patients.

Future research is needed to better identify possibly longitudinal changes in network controllability related to specific clinical outcome in both earlier and later stages of brain reorganizaion after brain damages (Anderson et al. 2011).

**Methodological considerations**

In this work, we exploited the step-wise target controllability framework (Bassignana et al. 2021), which relies on a linear time invariant (LTI) dynamics and is based on the Kalman rank condition. While it is known that the brain presents a nonlinear dynamics, the study of linear models has proved to be beneficial in improving our understanding (Gu et al. 2015; Liu and Barabási 2016; Tang and Bassett 2018). Specifically, the controllability of a linearized model can inform on the controllability of the nonlinear model (Slotine and Li 1991).

To study the controllability of brain networks efficiently, we gave a directionality to the connectomes. Despite the fact that it is not currently possible for neuroimaging techniques to discern the directionality of bundles of axons, it is known that each neuron propagates signals through a well-defined direction from the soma to the axon terminal. Previous efforts to direct a connectome relied on the hypothesis that, given a set of brain networks, edges present for all participants are the oldest, and any new edge would be directed from the new node to the existing cluster (Kerepesi et al. 2016). However, a limitation of this method is that it is strictly dependent on the initial set of networks, and the procedure would not be easily scalable. Other methods based on local navigation and communicability were devised to infer the directionality of neural signaling, but since they operate best for nodes connected by longer paths, they are not well-suited to perform inference for structurally connected nodes.
networks consisted of 188 nodes corresponding to functional and functional (fMRI) data. Both structural and functional data were acquired from 171 participants, aged from 5 to 85 (Brown et al. 2012).

We used already processed brain network data from the Human Connectome Project (HCP) (Seguin et al. 2019). Our approach was instead inspired by the diffusion processes taking place in the connectome (Worrell et al. 2017; Gofri et al. 2013; Avena-Koenigsberger et al. 2018; Raj et al. 2012; Abdelnour et al. 2018) and preserves the hierarchical and modular properties of the anatomical pathways.

Finally, it is important to mention that the obtained results refers to the specific way we have selected the target systems and and ranked the nodes therein contained, and should not be generalized to other possible choices. By adopting an “anatomical proximity” criterion, some regions that could be functionally associated to the frontal lobe, e.g. the anterior cingulate cortex ACC, have been instead assigned to the limbic system. The original dataset did not contain subcortical areas, such as amygdala, caudate nucleus, and hypothalamus (Catani et al. 2013), which are known to be tightly related to the limbic system. Future research will therefore be important to validate the obtained results on different brain atlases and target system selection. Furthermore, more rigorous anatomical and circuit-level information from histological and causal experiments can better elucidate the robustness of our results obtained from noninvasive neuro-imaging (Dubois et al. 2015; Schilling et al. 2018).

Conclusions

In this study, we presented a method to quantify the ability of candidate driver nodes to drive the state of a target set in directed brain networks. The obtained results revealed that sensorimotor areas are theoretically inclined to control different target systems, while regions in the temporal lobe were negatively impacted by age and by simulated damages to the network. These results are in line with the general claim of a dominant gradient of cortical organization with sensory-motor and association regions at opposing ends (Huntenburg et al. 2018; Malkinson et al. 2021). We hope that further developments of network controllability measures will contribute to the identification of the key nodes in biological networks to better identify targets of brain stimulation to counteract human diseases.

Methods

Structural and functional brain networks

We used already processed brain network data from the NKI-Rockland database (Nooner et al. 2012), and selected 171 participants, aged from 5 to 85 (Brown et al. 2012). For each participant, we had access to both structural (DTI) and functional (fMRI) data. Both structural and functional networks consisted of 188 nodes corresponding to functional regions of interest (ROIs) established with a spatially constrained spectral clustering method (Craddock et al. 2012). All related information including node labels and spatial position can be accessed via the USC Multimodal Connectivity Database http://umcd.humanconnectomeproject.org/umcd/. We also provided a compacted version of this information in a dedicated supplementary file (File S1). Note that some ROIs had been split in different parts. In this case, we added a suffix number at the end of the label to specify its relative position along the longitudinal axis of the brain (i.e. higher numbers, more caudal positions).

Directing structural brain networks

We directed the structural connectomes in order to study their controllability properties in a more efficient way, and we used the information from fMRI brain networks to establish a hierarchy among the nodes in the target systems. Starting from the DTI network, first we applied a logarithmic transformation (log (w + 1)) to make the weights more homogeneous. Then, we performed a biased random walk (Gómez-Gardeñes and Latora 2008) to direct each edge from the node with lower strength to the node with higher strength. The probability \( P_{ij} \) to go from node \( i \) to node \( j \), can be computed as

\[
P_{ij} = \frac{w_{ij}}{\sum_h w_{ih}}.
\]

where \([w]_{ij}\) is the symmetric, weighted adjacency matrix of the structural network. For each pair of nodes \( i \) and \( j \), we had two directed edges with weights \( P_{ij} \) and \( P_{ji} \). We chose one direction by keeping only the highest probability (we kept both if they were equal), thus drastically reducing the presence of loops in the network.

The choice of removing some links was inspired by the works on the minimum spanning tree (MST) procedure applied to brain networks (Tewarie et al. 2015). Similarly to our strategy, the MST filtering procedure eliminates any loop in the network, yet important information can be obtained on the brain network structure and function with implication in aging (van Dellen et al. 2018). Despite such background, our choice still remains a modeling strategy that favors information propagation toward higher degree nodes. Note that the resulting effect is in line with the evidence that hubs in real networks tend to have less control power (mechanistically exerted by outgoing links), as they instead need to be efficiently accessed to control the rest of the network (Liu et al. 2011). As for the reduction of loops, it is important to stress that this might lead to underestimate the number of controllable nodes, but not to introduce false positive results. This is because of the underlying k-walk theory by which
a driver-target configuration is controllable if the length of the path from the driver to each target is unique (Gao et al. 2014).

### Step-wise target controllability

We implemented the step-wise target controllability framework (Bassignana et al. 2021), that analyses the single-input target controllability problem, in which the interest is to study the role of a single driver node in controlling a target set of the system. We assumed the linear time invariant (LTI) dynamics

\[
x(n) = Ax(n) + Bu(n), \quad y(n) = Cx(n),
\]

where \( x(n) \in \mathbb{R}^N \) describes the state of each node at time \( n \), \( A \) is the adjacency matrix of the network, \( B \in \mathbb{R}^{N \times N} \) specifies the driver node that will receive an external input, \( u(n) \in \mathbb{R}^N \) is its external input (or control) signal, \( y(n) \in \mathbb{R}^S \) is the output vector, and \( C \in \mathbb{R}^{S \times N} \) is the output matrix identifying the target nodes.

Such a system is controllable if it can be guided from any initial state to any desired final state in finite time, with a suitable choice of input.

A necessary and sufficient condition to assess the controllability of Eq. 2, is that the controllability matrix \( Q \)

\[
Q = [B \ AB \ A^2B \ \cdots \ A^{N-1}B]
\]

has full row rank, i.e. \( \text{rank}(Q) = N \). That is the Kalman rank condition, which basically verifies the existence of linearly independent rows in \( Q \) (Kalman 1963; Rugh and Kailath 1995). If so, the driver node can reach and control the dynamics of all the other nodes through independent walks of length \( N - 1 \) at maximum.

If it is of interest to control only a target set \( T \) of the network, specified in \( C \) and consisting of \( S \leq N \) nodes, then Eq. 2 can be reduced into a target controllability matrix \( Q_T = CQ \), where \( C \) filters the rows of interest corresponding to the targets. Now, the rank of \( Q_T \) gives the number \( \tau \leq S \) of nodes in the target set that can be controlled by the driver.

To identify a driver-target configuration, we further introduce a hierarchy among the target nodes, so that we can order and relabel them from the most important one to the least, i.e. \( t_1 > t_2 > \cdots > t_5 \). Then we perform the following step-wise procedure for each candidate driver node:

- **Step 1. Initialization**
  - Create a temporary empty target set \( T' \leftarrow \{ \} \)
  - Set the number of controllable targets \( \tau \leftarrow 0 \)

- **Step 2. Repeat until termination criteria are met.** For \( j \leftarrow 1, \ldots, S \) do
  - Add the \( j \)-th target node to the target set \( T' \leftarrow T' \cup \{t_j\} \)
  - Build the subgraph containing the nodes on walks from the driver to the targets in \( T' \)
  - Compute the rank of the target controllability matrix \( Q'_T \)
  - If \( \text{rank}(Q'_T) \) is full then \( \tau \leftarrow \tau + 1 \) else \( T' \leftarrow T' \setminus \{t_j\} \)
  - \( j \leftarrow j + 1 \)

- **Step 3. Output \( \tau \) and \( T' \)**

Eventually, the target control centrality \( \tau \) is the number of controllable targets in \( T' \), and the set \( T' \) contains the \( \tau \) controllable targets with highest ranking.

### Application to brain networks

In this specific application, we assumed that the states of the nodes/ROIs were influenced by the adjacency matrix corresponding to the directed structural connectome. The target sets were the structural systems (frontal, limbic, temporal, sensorimotor, parietal, occipital, Fig. S1). ROIs in the target system were ranked according to the group-averaged node strengths obtained from the fMRI functional brain network (Fig. 1, File S1).

More precisely, we ranked the nodes in the target set \( T \) in a descending order from the quantity \( \frac{1}{M} \sum_m s_i^{(m)} \), where \( s_i^{(m)} \) is the node strength (i.e. the weighted sum of all the connections) of the node \( i \) obtained from the fMRI functional network of the participant \( m \), and \( M \) is the number of participants in the study. Node strengths quantify the tendency of brain areas to act as hubs which are crucial constituents of the overall information integration (van den Heuvel and Sporns 2013).

The target control centrality \( \tau \) of each node is obtained via the step-wise procedure described above and gives the corresponding highest ranked controllable configuration of target nodes. To obtain a more robust estimation, we derived an integrated measure of target control centrality by averaging the results from the connectomes thresholded with different connection densities (De Vico Fallani et al. 2014). Specifically, for each participant, we retained the strongest links so that we have networks with mean node degree \( k \) ranging from 1 to 14. This upper limit corresponded to the lowest number of links found after directing the connectomes.

### System regulation score

To quantify how the target control centrality of a system is globally distributed across the other target systems we introduced the so-called system regulation score \( R \). Given two brain systems \( i \) and \( j \) the regulation score reads as

\[
R = \frac{1}{N(N-1)} \sum_{i,j} \text{system regulation score}_{ij}
\]
\[ R_y = \frac{1}{|S^0|} \sum_{k \in S^0} \tau_k^{(j)}, \quad (4) \]

where \( S^0 \) is the reference system \( i \), \( V \) is the set of all \( N \) nodes in the brain network, and \( \tau_k^{(j)} \) is the target control centrality of each node in the system \( i \) over the target system \( j \). When \( i = j \), we specifically talk about self-regulation.

**Statistical analysis**

All statistical analysis were performed with a statistical threshold of \( p = 0.05 \), adjusted via a false-discovery rate (FDR) procedure in the case of multiple tests (Benjamini and Hochberg 1995).

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**Data availability statement** All the experimental data used in this work are fully accessible from the NKI-Rockland database (Nooner et al. 2012).

**Declarations**

**Conflict of interest** Authors declare no conflict of interest.

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