

Supplementary information

Supplementary material

The maximum firing rate of the three nodes prior to the *silencing* ($PS-MFR_{max}$) was monitored to quantify the potential impact of a local manipulation. With regard to the manipulated nodes, we also defined the local manipulation weighted degree (LWD) as the sum of weighted incoming and outgoing connections of the manipulated nodes in the structural connectivity (SC). To compute the MFR of the most active nodes we first ranked the nodes based on their firing rate and then averaged the MFR over groups of consecutive 4 to 7 ‘ranked’ nodes. Since the results were quite comparable irrespective of the size of the groups we report the results only for 5 nodes.

Supplementary results

S1. Pre-silencing activity and connectivity is predictive of the outcome of node manipulation

Further exploring the determinants of the impact of local node manipulations, we investigated whether structural and functional properties prior to silencing could be predictive of the observed impact on both model activity and complexity metrics. First, we implemented a linear model (Fig. S1A) describing the MFR_{Δ} of all nodes as a function of the $PS-MFR_{max}$ and found a significant negative relationship ($r=-0.8$, $p=2\cdot 10^{-5}$). Next, we computed the linear correlation between $PS-MFR_{max}$ and LZc (Fig. S1B) and once again observed a significant negative correlation ($r=-0.64$, $p=0.002$). Then, similar to previous studies (Aerts et al. 2016) showing that silencing of central nodes had a greater impact on network activity, we related the weighted degree of the manipulated nodes (LWD, see Supplementary material) to the same metrics (Fig S1C, D). While the correlation was non-significant for all variables ($p>0.05$), including LWD as a regressor alongside $PS-MFR_{max}$ (Fig. S1E, F) resulted in an improved description of the MFR_{Δ} ($R^2=0.75$, $R^2_{adjusted}=0.72$, $p=7\cdot 10^{-6}$; $\beta_{PS-MFR_{max}}=-0.266$, 95% CI [-0.345, -0.187]; $\beta_{LWD}=-0.0033$, 95% CI [-0.0058, -0.0008]) and LZc ($R^2=0.62$, $R^2_{adjusted}=0.58$, $p=0.0002$; $\beta_{PS-MFR_{max}}=-0.0023$, 95% CI [-0.0033, -0.0014]; $\beta_{LWD}=-0.000043$, 95% CI [-0.000072, -0.000014]).

S2. Relation between PCI and the source entropy

In order to exclude the presence of a trivial relationship between the source entropy (H_{src}) and the perturbational complexity index (PCI) we performed additional analysis. Importantly, we found that for a given stimulus there was no clear relation between H_{src} and PCI (Fig S3A, B, C). Instead, only when all stimuli, local manipulations and averages across resamples (i.e. mean across PCI, mean across H_{src}) were reported together a significant linear trend in the data was found (Fig S3D, $r=-0.29$, $p=4\cdot 10^{-6}$). The latter shows that complex patterns do not necessarily increase with a larger amount of significant activations of the post-stimulus response. Note that, while PCI decreased significantly with respect to control across resamples (190 out of 240 configurations – 12 stimuli x 20 local manipulations – $p<0.05$; corresponding to the amount of significant cases of Fig. S2), H_{src} instead, either increased or decreased with respect to control condition.

S3. Comparing spontaneous and perturbational metrics

To compare the outcome of spontaneous and perturbational complexity analysis, we summarized the relationship between the various metrics by the Pearson correlation coefficient (Table S4). MFR correlated significantly with all complexity indices, albeit more strongly with LZc, highlighting the important role of suitable network activity in expressing complex cortical dynamics. Notably, PCI and LZc did not correlate (for 11 out of 12 stimulations, $p>0.05$). In addition, as with LZc, we performed multivariate regressions to relate the spontaneous metrics to PCI. Specifically, we modelled PCI as a function of MFR and the activity correlation CC_{IFR} , and we found that the slope

coefficient of CC_{IFR} (β_{CC}) was not significantly different from zero across stimulations (8 out of 12 had CI falling around the zero value), suggesting that PCI is not much sensitive to synchronous activity. Additionally, unlike LZc, PCI was not simply described by the functional ($PS-MFR_{max}$) attributes of the silenced nodes (for 10 out of 12 stimulations, $p>0.05$).

S4. LZc topography

Interestingly, the LZc topography (Fig. S6B) was characterized by higher R^2 values in the intact hemisphere (IH) instead of the manipulated one (MH) as it occurred for PCI. We hypothesized that this result was not correlated to the activity of the intact hemisphere (IH) and, in order to verify this, we restricted the computation of LZc to the manipulated hemisphere (MH) which resulted in a strong correlation with LZc ($r=0.97$, $p=8\cdot 10^{-13}$; Fig S6C left panel). Thus the MH alone follows the same trend of the whole brain LZc when silencing the different nodes of the connectome. Subsequently, to exclude the contribution of activities bouncing from one hemisphere to the other we calculated LZc on a truncated connectome, where connections from IH to MH were removed (IMH_{cut}). Again we found that LZc computed on the truncated connectome correlated with LZc computed on the entire connectome ($r=0.88$, $p=2\cdot 10^{-7}$; Fig. S6C right panel). Next, to clarify the reasons of the correlation between IH and LZc, we examined how the MH manipulations affected IH. This analysis yielded two key observations: 1) the nodes of the IH covaried across local manipulations (average Pearson correlation coefficient across nodes $\langle r \rangle = 0.9$, Fig. S6D), indicating that the latter had a non-specific impact on IH, 2) the activity in the intact hemisphere (MFR_{IH}) correlated strongly ($r=0.98$, $p=4\cdot 10^{-15}$) with the activity of the most firing nodes of MH ($MFR_{MH(most\ active)}$; Fig. S6E top panel). Interestingly, the correlation of LZc with MFR_{MH} also increased with the most active nodes ($r=0.81$, $p=8\cdot 10^{-6}$; Fig. S6E bottom panel).

Finally, we conclude that: 1) LZc can be largely explained by the manipulated hemisphere, and 2) $MFR_{MH(most\ active)}$ drive the covariation between LZc and MFR_{IH} .

Supplementary tables

Table S1. Labels of the cortical nodes and their description in Hconn. The stimulated region is reported in bold (14 adjacent nodes within this region are stimulated simultaneously in all conditions).

Label	Description
BSTS	Bank of the superior temporal sulcus
CAC	Caudal anterior cingulate cortex
CMF	caudal middle frontal cortex
CUN	Cuneus
ENT	Entorhinal cortex
FP	Frontal pole
FUS	Fusiform gyrus
IP	Inferior parietal cortex
IT	Inferior temporal cortex
ISTC	Isthmus of the cingulate cortex
LOCC	Lateral occipital cortex
LOF	Lateral orbitofrontal cortex
LIN	Lingual gyrus
MOF	Medial orbitofrontal cortex
MT	Middle temporal cortex
PARC	Paracentral lobule
PARH	Parahippocampal cortex
POPE	Pars opercularis
PORB	Pars orbitalis
PTRI	Pars triangularis
PCAL	Pericalcarine cortex
PSTC	Postcentral gyrus
PC	Posterior cingulate cortex
PREC	Precentral gyrus
PCUN	Precuneus
RAC	Rostral anterior cingulate cortex
RMF	Rostral middle frontal cortex
SF	Superior frontal cortex
SP	Superior parietal cortex
ST	Superior temporal cortex
SMAR	Supramarginal gyrus
TP	Temporal pole
TT	Transverse temporal cortex

Table S2. Larter & Breakspear parameters. The parameters changed from Alstott et al. 2009 are indicated in bold.

Parameter	Description	Value in Dconn	Value in Hconn
g_{Ca}	Conductance of population of Ca channels	1.1	1.1
V_{Ca}	Ca Nernst potential	1	1.1
r_{NMDA}	Ratio of NMDA to AMPA receptors	0.25	0.25
g_{Na}	Conductance of population of Na channels	6.7	6.7
V_{Na}	Na Nernst potential	0.53	0.53
a_{ee}	Excitatory-to-excitatory synaptic strength	0.35	0.5
g_K	Conductance of population of K channels	2.5	2.5
V_K	K Nernst potential	-0.7	-0.7
g_L	Conductance of population of leak channels	0.7	1.1
V_L	Nernst potential of leak channels	-0.5	-0.5
a_{ie}	Inhibitory-to-excitatory synaptic strength	2	2
a_{ne}	Non-specific-to-excitatory synaptic strength	1	1
I	Subcortical input strength	0.3	0.3
b	Time constant scaling factor	0.1	0.1
a_{ni}	Non-specific-to-inhibitory synaptic strength	0.42	0.4 (0.4023 in the left hem)
a_{ei}	Excitatory-to-inhibitory synaptic strength	2	1
T_{Ca}	Threshold potential for Ca channels	-0.01	-0.01
T_{Na}	Threshold potential for Na channels	0.26	0.26
T_K	Threshold potential for K channels	0	0
δ_{Ca}	Variance of Ca channels threshold	0.15	0.15
δ_{Na}	Variance of Na channels threshold	0.15	0.15
δ_K	Variance of K channels threshold	0.4	0.4
φ	Temperature scaling factor	0.7	0.7
τ_K	Time constant for K relaxation time	1	1
QV_{max}	Maximal firing rate for excitatory populations	1	1
V_T	Threshold potential for excitatory neurons	-0.1	-0.1
δ_V	Variance of excitatory threshold	0.65	0.65
QZ_{max}	Maximal firing rate inhibitory populations	1	1
Z_T	Threshold potential for inhibitory neurons	0	0
δ_Z	Variance of inhibitory threshold	0.6	0.6
C	Strength of excitatory coupling and balance between internal and global dynamics	0.1	0.1

Table S3. Local manipulation labels in the Hconn connectome. The labels of the local manipulation and the corresponding nodes silenced in the Hconn connectome. The number of silenced nodes within the specified region is given in brackets (e.g., in HL1: nodes CUN1, CUN2, ..., CUN7; ISTC1,..., ISTC4; etc.).

Local manipulation label	Nodes
HL1	CUN (7), ISTC (4), LING (3), PCAL (5), PCUN (19), SP (2)
HL2	CMF (5), POPE (1), PREC (16), PSTC (16), SMAR (2)
HL3	FP (2), LOF (15), MOF (11), PORB (1), RAC (4), RMF (4), SF (3)
HL4	ENT (2), FUS (5), IT (9), LOF (2) MT (6), PARH (1), ST (12), TP (3)
HL5	BSTS (7), MT (4), PSTC (5), SMAR (6), ST (15), TT (3)
HL6	BSTS (5), IP (8), MT (2), PSTC (3), SMAR (14), ST (8)
HL7	POPE (4), PREC (11), PSTC (11), SMAR (2), ST (11), TT (1)
HL8	FUS (3), IP (18), IT (1), LOCC (10), MT (2), PCAL (1), PCUN (1), SP (4)
HL9	CUN (1), FUS (5), IP (5), ISTC (3), IT (1), LING (12), LOCC (1), MT (1), PARH (1), PCAL (3), PCUN (5), SP (2)
HL10	CUN (2), FUS (6), LING (11), LOCC (13), PCAL (8)
HL11	FUS (10), IP (4), IT (2), LING (4), LOCC (16), MT (2), PCAL (2)
HL12	LOF (15), POPE (2), PORB (5), PTRI (8), RMF (4), ST (4), TP (2)
HL13	BSTS (5), FUS (6), IP (13), ISTC (1), IT (5), LING (2), LOCC (3), MT (5)
HL14	BSTS (4), FUS (12), ISTC (2), IT (5), LING (7), MT (1), PARH (6), ST (2), TT (1)
HL15	CUN (4), FUS (3), LING (8), LOCC (15), PCAL (9), SP (1)
HL16	CMF (2), LOF (4), POPE (10), PREC (5), PTRI (7), RMF (12)
HL17	LOF (10), POPE (2), PORB (6), PTRI (8), RMF (7), ST (6), TP (1)
HL18	LOF (5), POPE (10), PORB (4), PREC (1), PTRI (8), RMF (12)
HL19	CMF (5), POPE (9), PTRI (8), RMF (16), SF (2)
HL20	CUN (2), IP (14), ISTC (1), LING (1), LOCC (3), PCAL (4), PCUN (7), SP (8)

Table S4. Pearson correlation between spontaneous and evoked metrics. The Pearson correlation coefficients between different metrics are computed across local manipulations. The correlation values between PCI and the other metrics are reported as mean $\pm$ SD computed over the 12 Pearson correlation coefficients (1 per stimulus). Asterisks indicate level of statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns: non-significant.

	PCI	LZc	MFR	CC _{IFR}
PCI	1.000			
LZc	0.23 $\pm$ 0.12 (* in 1 case)	1.00		
MFR	0.56 $\pm$ 0.09 (* in 11 cases)	0.69***	1.00	
CC _{IFR}	0.39 $\pm$ 0.13 (* in 4 cases)	-0.55**	0.21 ^{ns}	1.00

Supplementary figures

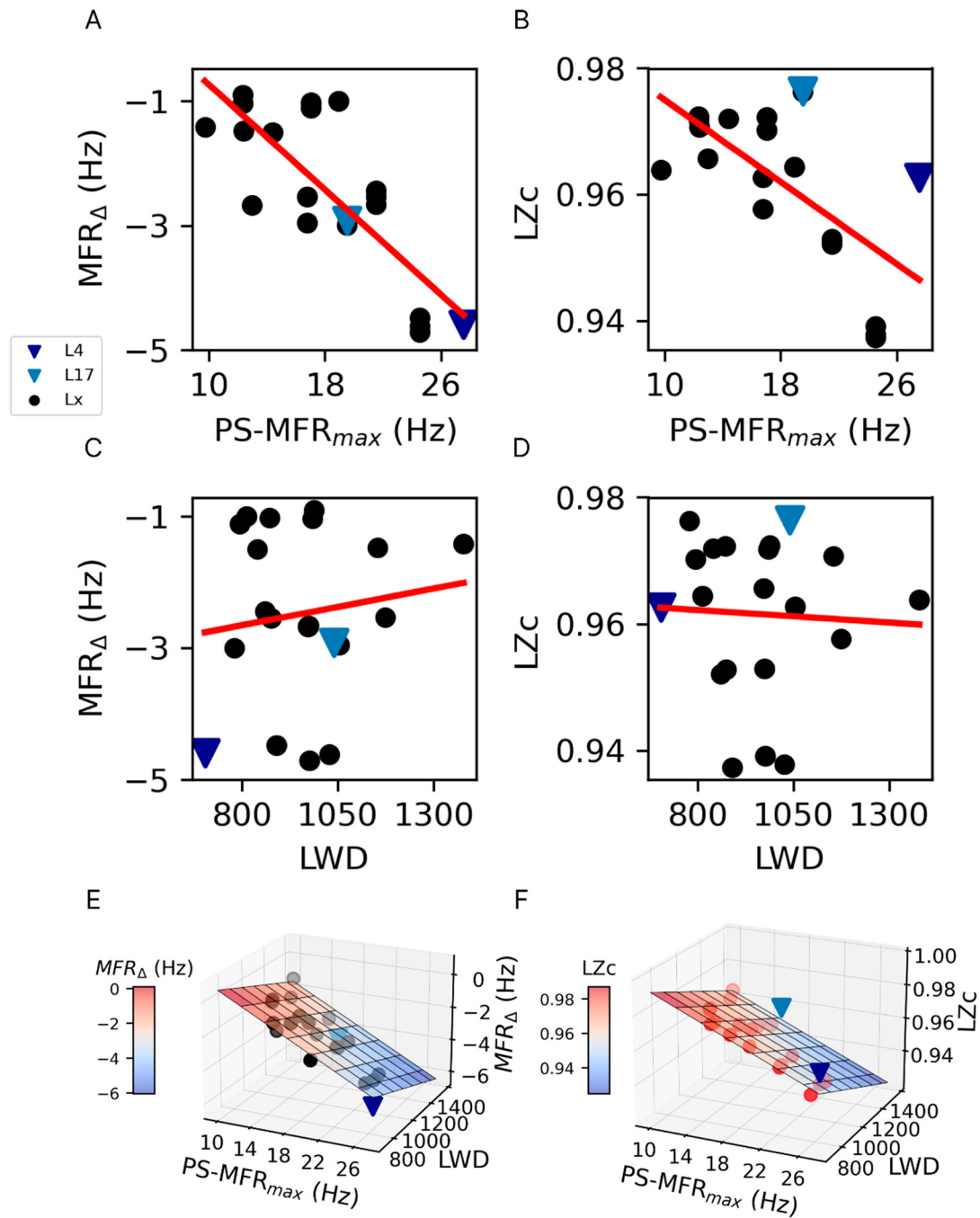


Figure S1. Pre-silencing activity and connectivity correlated with the outcome of node manipulation A) Linear regression of the MFR_{Δ} in all nodes with respect to $PS-MFR_{max}$ ($r=-0.8$, $p=2 \cdot 10^{-5}$). B) Linear regression of LZc with respect to $PS-MFR_{max}$ ($r=-0.64$, $p=0.002$). C) Linear regression of the MFR_{Δ} in all nodes with respect to LWD ($p=0.57$). D) Linear regression of LZc with respect to LWD ($p=0.83$). E) Linear regression of the MFR_{Δ} in all nodes with respect to the independent $PS-MFR_{max}$ and the weight degree of the locally manipulated nodes (LWD) ($R^2=0.75$, $R^2_{adjusted}=0.72$, $7 \cdot 10^{-6}$). F) Linear regression of LZc with respect to the independent $PS-MFR_{max}$ and LWD ($R^2=0.62$, $R^2_{adjusted}=0.58$, $p=0.0002$).

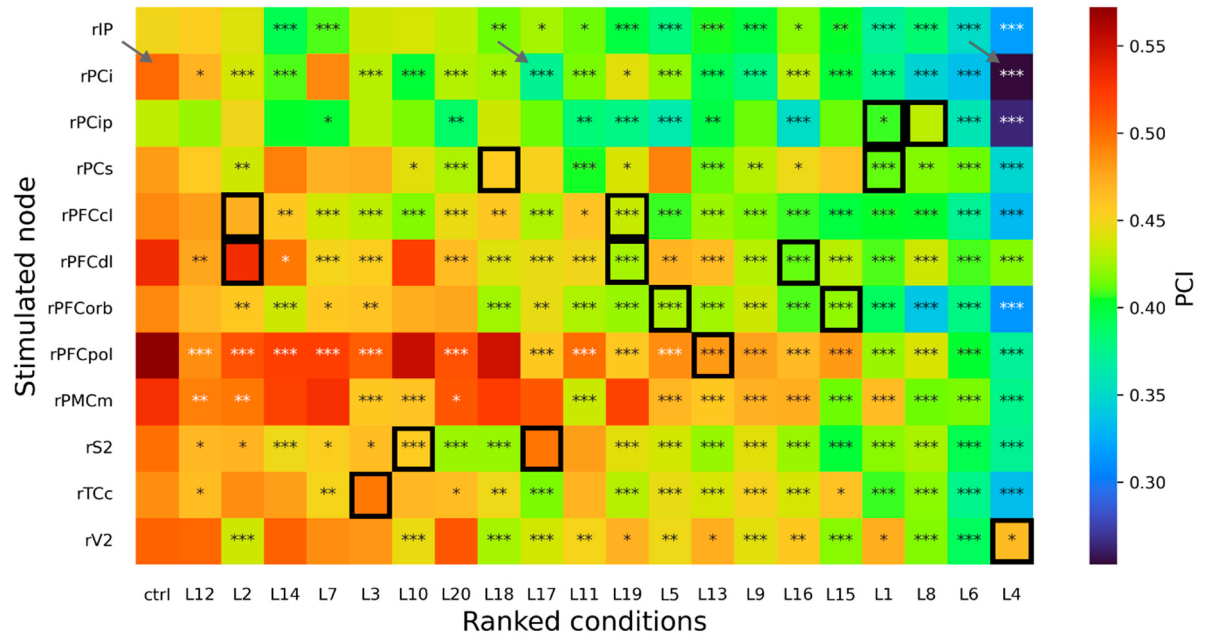


Figure S2. PCI decreased significantly in most local manipulations. PCI values are given for each combination of stimulus (rows) and local manipulation/control (columns). The conditions (control and local manipulations) are sorted in descending order according to the average PCI value computed across stimulation sites. The grey arrows indicate the ctrl, L4 and L17 conditions analysed in the main text (section 3.2.1) and black boxes mark local manipulations that were changed as they included the stimulated node (see methods, section 2.1.4). Asterisks mark significant differences of each local manipulation compared to the control with the same stimulated node (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ANOVA and post hoc pairwise T test with Benjamini-Hochberg correction).

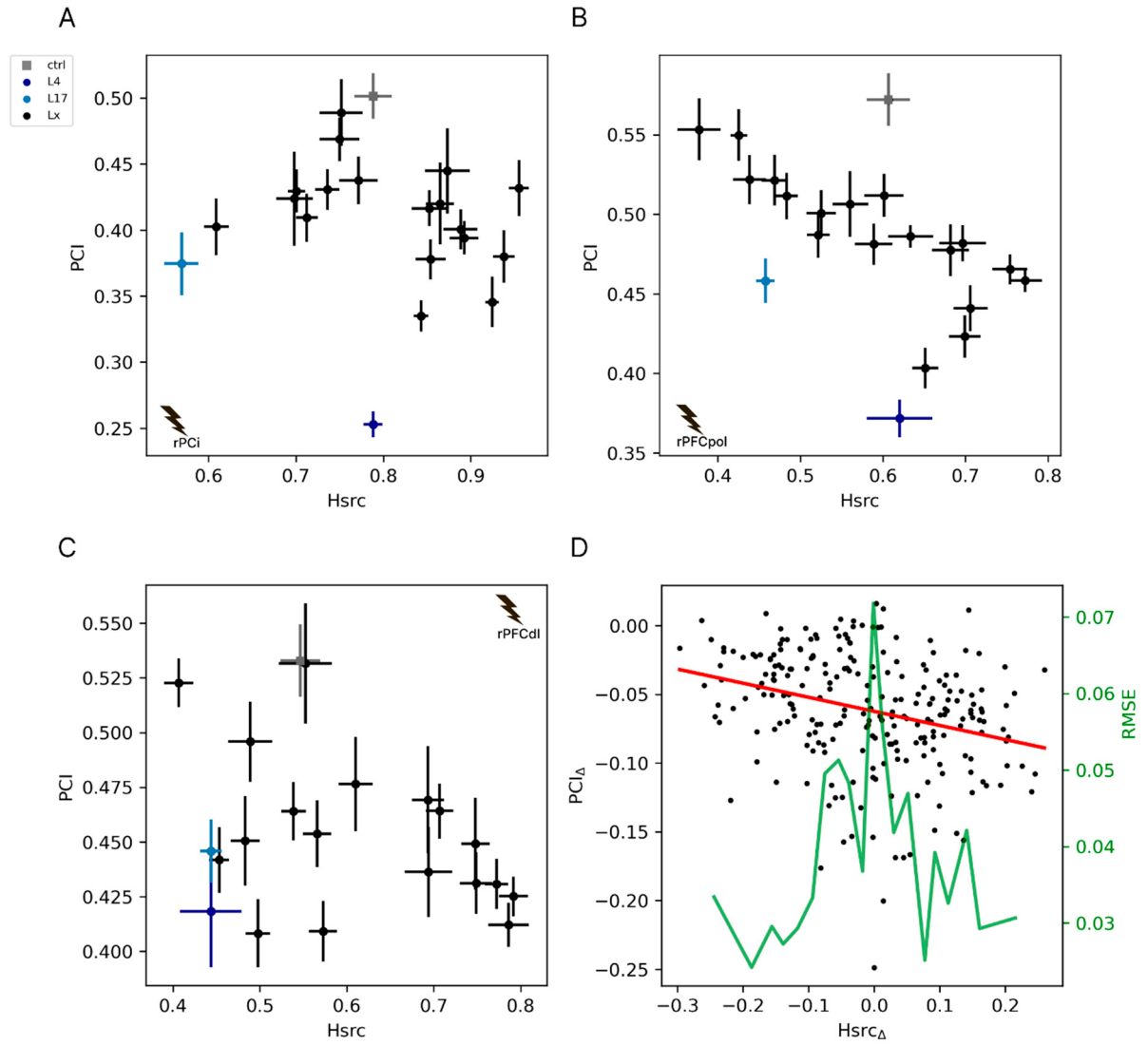


Figure S3. Non-trivial relation between PCI and Hsrc. Relation between PCI and Hsrc, for each local manipulation, in the stimulation of rPCi (A), rPFCpol (B) and rPFCdl (C). The error bars represent 2 SEM computed over resamples of the trials (10 resamples of 300 trials each). D) Summary plot for all stimulation sites and silencing conditions. A significant negative correlation between Hsrc $_{\Delta}$ and PCI $_{\Delta}$ is found in the linear regression ($r=-0.29$, $p<0.001$). The green curve represents the root mean squared error (RMSE) from the fit line. The Hsrc $_{\Delta}$ distribution was subdivided in 20 equi-populated bins. The x-values of the curve are the central value of each bin and the y-values are the corresponding RMSEs. PCI $_{\Delta}$ and Hsrc $_{\Delta}$ are differences with respect to control condition for a given stimulation site (e.g. stimulation of rPCi: PCI $_{\Delta}(\text{local manipulation}) = \langle \text{PCI}_{\text{local manipulation}} \rangle - \langle \text{PCI}_{\text{ctrl}} \rangle$ and Hsrc $_{\Delta}(\text{local manipulation}) = \langle \text{Hsrc}_{\text{local manipulation}} \rangle - \langle \text{Hsrc}_{\text{ctrl}} \rangle$, where $\langle \dots \rangle$ indicates mean across resamples).

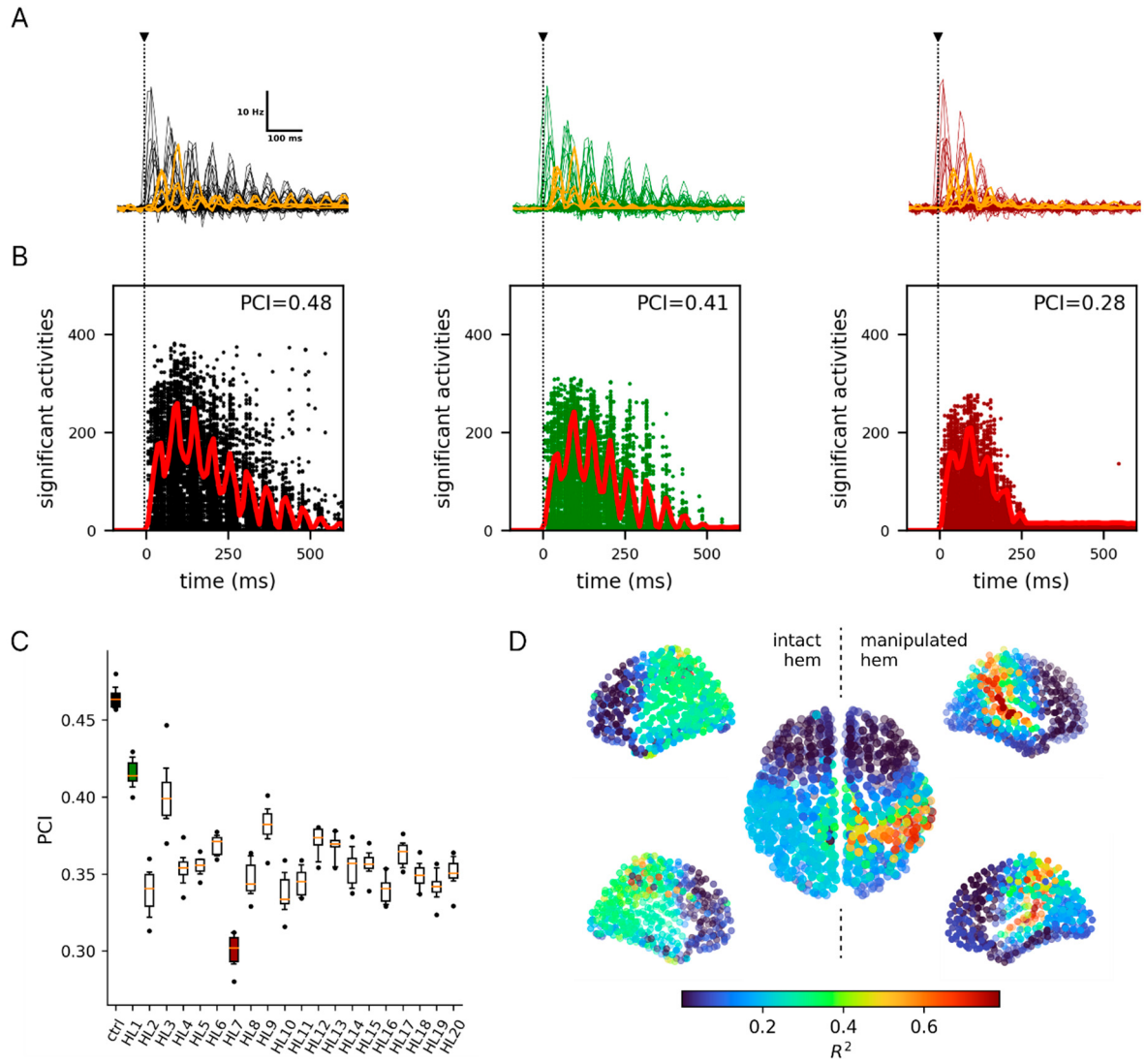


Figure S4. Impact of local manipulations on perturbational complexity in Hconn. A) The temporal courses of the instantaneous firing rate with respect to baseline (averaged across trials, $\langle \Delta IFR \rangle$) are reported for all regions of the stimulated hemisphere and separately for the representative conditions: ctrl (black), HL1 (green) and HL7 (dark red). For each condition, the highest five $\langle \Delta IFR \rangle$ s (quantified as the total activity in the interval [0,500] ms) of the non-stimulated hemisphere (orange traces) are also reported. The vertical dotted black line marks the time of the stimulus. The IFR traces of the 66 cortical regions are obtained by averaging the IFR of the nodes belonging to the respective region. B) The corresponding sorted binary spatiotemporal matrices of significant activities highlight the impact of the local manipulations with respect to the ctrl condition (the red line is the sum of significant activity over time). C) The Perturbational complexity index (PCI) decreases significantly in all silencing conditions (for each $p < 0.000001$, ANOVA and post hoc pairwise T test with Benjamini-Hochberg correction). D) Topography of the R^2 values over the brain map showing the prevalence of higher values at posterior nodes. R^2 values are obtained as in Fig. 4 (main figure), performing a linear regression, for each node, fitting PCI versus the node's pre-stimulus MFR.

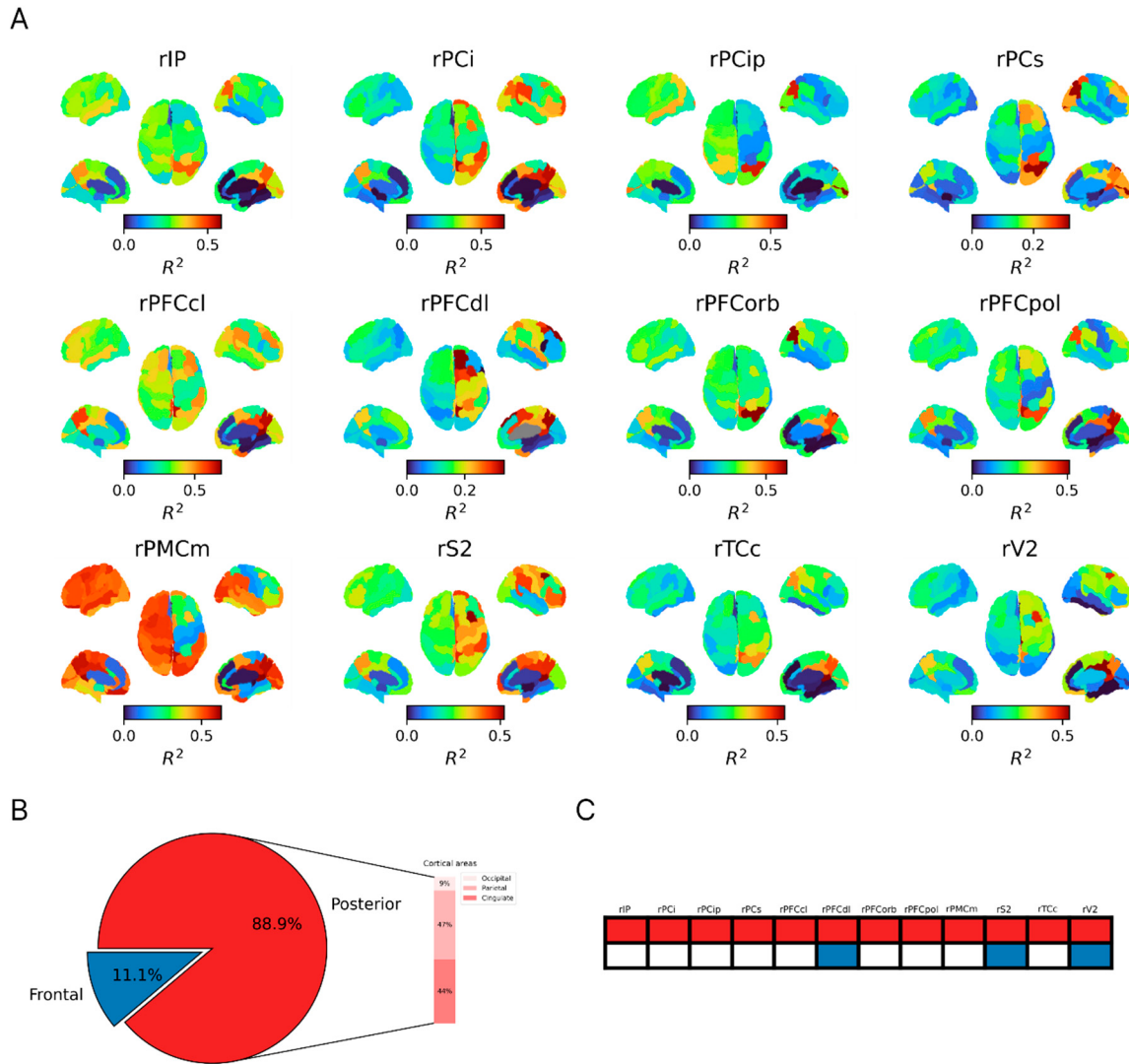


Figure S5. The PCI-R² topographies for each stimulation site confirm the importance of the posterior regions A) R² values over the brain map for each stimulation site (reported above the brain maps). For each node, the R² values are relative to the linear regressions of PCI versus spontaneous MFR across conditions (control and local manipulations). B) Occurrence of the posterior and frontal regions. For each stimulus the highest three R² values are considered (for a total of 3x12 R²-ROIs). C) For each stimulation site (rIP, ..., rV2) the presence of the three highest R² values is monitored. Whenever a posterior and/or a frontal node is part of the three highest R² values the corresponding box is coloured in red and/or blue. The nodes belonging to the parietal, occipital, temporal, posterior cingulate (posterior and retrosplenial) cortices in Dconn were considered posterior, for a total of 39 nodes. The remaining 37 nodes were considered frontal.

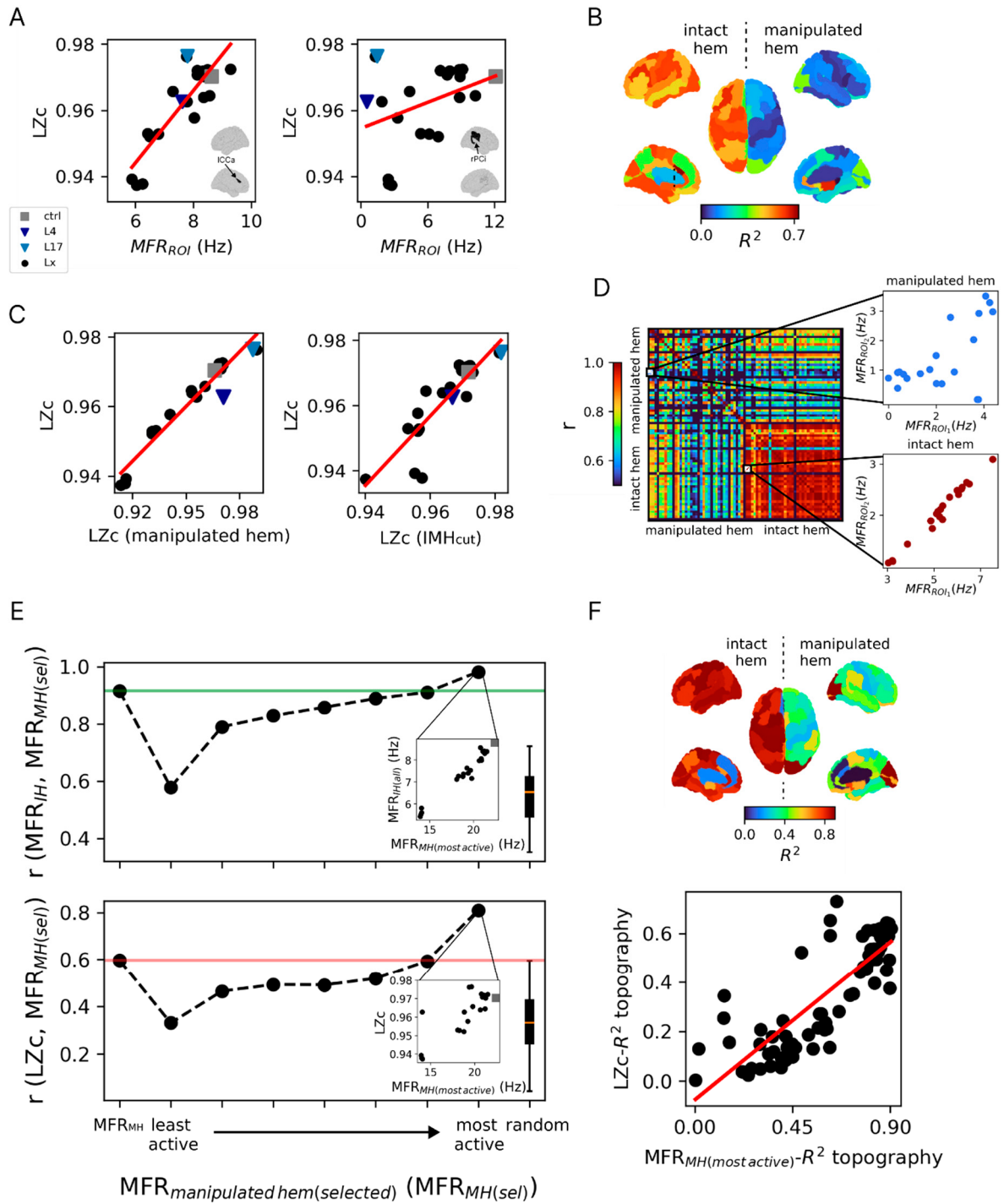


Figure S6. Characterization of the LZc- R^2 topography. A) Linear regression of LZc (NC) versus MFR for the example ROIs ICCa and rPci (LZc: ICCa- $R^2=0.732$, $p=10^{-6}$, rPci- $R^2=0.131$, $p=0.11$). B) Topographies of the coefficient of determination (R^2) of the linear regressions for LZc. C) Left panel: correlation ($r=0.97$, $p=8 \cdot 10^{-13}$) between LZc (all nodes) and LZc computed only over the manipulated hemisphere (MH). Right panel: correlation ($r=0.88$, $p=2 \cdot 10^{-7}$) between LZc (all nodes) and LZc with connections from the Intact to the manipulated hemisphere removed (IMH_{cut}). D) Correlation matrix of node activity (MFR) across local manipulations. The intact and the manipulated hemispheres are specified in the figure. MFR scatter plots for two exemplary nodes (ROI₁ and ROI₂) across local manipulations for the intact and the manipulated hemispheres. E) Top panel: Pearson correlation coefficient (r) calculated between the MFR of selected nodes in the manipulated hemisphere

($MFR_{MH(sel)}$) and the MFR of the intact hemisphere (MFR_{IH}). 'Random' denotes a random sampling of 5 nodes (without replacement, 100 repetitions) and the boxplot of the corresponding correlation values between $MFR_{MH(random)}$ and MFR_{IH} are reported. The inset is relative to the scatter plot with the highest correlation between $MFR_{MH(most\ active)}$ and MFR_{IH} ($r=0.98$, $p=4\cdot 10^{-15}$). The horizontal green line marks the value of r ($=0.93$, $p=2\cdot 10^{-9}$) when all nodes of the manipulated hemisphere are selected (MFR_{MH}). Bottom panel: the same procedure is repeated with LZc instead of MFR_{IH} . The inset is relative to the scatter plot with the highest correlation between $MFR_{MH(most\ active)}$ and LZc ($r=0.81$, $p=8\cdot 10^{-6}$). The horizontal red line indicates the value of r ($=0.61$, $p=0.003$) when all nodes of the manipulated hemisphere are selected (MFR_{MH}). F) Top panel: the coefficients of determination of the linear regressions $MFR_{MH(most\ active)}$ (panel E) vs MFR_{ROI} are reported in the topographic map. Bottom panel: the R^2 values of the linear regressions $MFR_{MH(most\ active)}$ vs MFR_{ROI} ($MFR_{MH(most\ active)}$ - R^2 topography, x-axis) and LZc vs MFR_{ROI} (LZc- R^2 topography, y-axis) correlated well ($r=0.83$, $p=10^{-19}$).

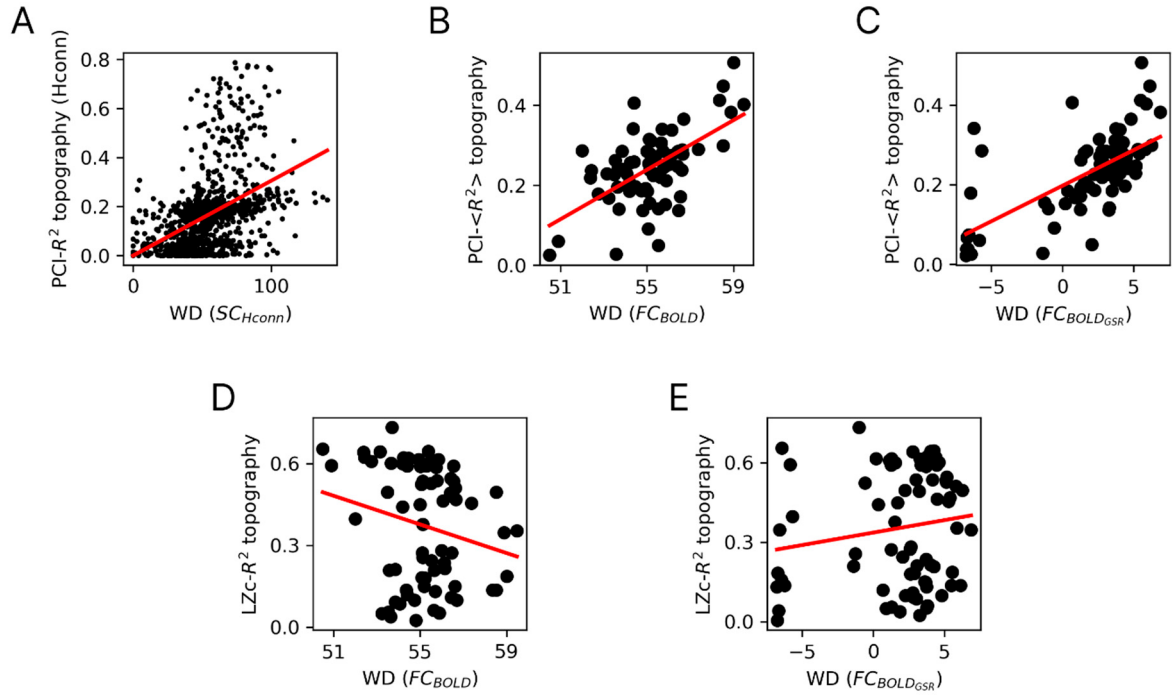


Figure S7 Network metrics of centrality correlate with complexity topographies. A) The weighted degree (WD) of structural connectivity (SC) nodes in Hconn correlated with the PCI-R² topography (Pearson correlation: $r=0.44$ $p=2 \cdot 10^{-49}$; spearman correlation: $\rho=0.51$, $p=4 \cdot 10^{-68}$). B) and C) The WD of the nodes of the functional connectivity extracted from the BOLD signal without or with global signal regression (GSR; FC_{BOLD}, FC_{BOLDGSR}, respectively) displayed a significant correlation with the PCI-<R^{2BOLD: $r=0.6$, $p=6 \cdot 10^{-8}$, FC_{BOLDGSR}: $r=0.65$, $p=10^{-10}$). D) and E) The same analysis showed a nonsignificant correlation between the WD and LZc-R² topography ($p=0.074$ and $p=0.17$, respectively). Each point is representative of a node in the network. In the panels B and D points with WD<50 (of the FC_{BOLD}) were considered outliers and excluded from the analysis. When all points are considered, comparable results are observed ($r=0.51$, $p=2 \cdot 10^{-6}$; $p=0.081$ for panels B and D, respectively).}