

Cingulo-Opercular Control Network Supports Disused Motor Circuits in Standby Mode

Authors:

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Abstract

1 Whole-brain resting-state functional MRI (rs-fMRI) during two weeks of limb constraint
2 revealed that disused motor regions became more strongly connected to the cingulo-opercular
3 network (CON), an executive control network that includes regions of the dorsal anterior
4 cingulate cortex (dACC) and insula (1). Disuse-driven increases in functional connectivity (FC)
5 were specific to the CON and somatomotor networks and did not involve any other networks,
6 such as the salience, frontoparietal, or default mode networks. Censoring and modeling
7 analyses showed that FC increases during casting were mediated by large, spontaneous
8 activity pulses that appeared in the disused motor regions and CON control regions. During
9 limb constraint, disused motor circuits appear to enter a standby mode characterized by
10 spontaneous activity pulses and strengthened connectivity to CON executive control regions.

Significance

Many studies have examined plasticity in the primary somatosensory and motor cortex during disuse, but little is known about how disuse impacts the brain outside of primary cortical areas. We leveraged the whole-brain coverage of resting-state functional MRI (rs-fMRI) to discover that disuse drives plasticity of distant executive control regions in the cingulo-opercular network (CON). Two complementary analyses, pulse censoring and pulse addition, demonstrated that increased functional connectivity between the CON and disused motor regions was driven by large, spontaneous pulses of activity in the CON and disused motor regions. These results point to a previously unknown role for the CON in supporting motor plasticity and reveal spontaneous activity pulses as a novel mechanism for reorganizing the brain's functional connections.

Introduction

Disuse is a powerful paradigm for inducing plasticity that has uncovered key organizing principles of the human brain (2-5). Monocular deprivation revealed that multiple afferent inputs can compete for representational territory in the primary visual cortex (2). Competition between afferents also shapes the somatomotor system, and manipulations such as peripheral nerve deafferentation, whisker trimming, and limb constraint all drive plasticity in the primary somatosensory and motor cortex (3-5). Most plasticity studies to date have used focal techniques, such as microelectrode recordings, to study local changes in brain function. As a result, little is known about how behavior and experience shape the brain-wide functional networks that support complex cognitive operations (6).

34 The brain is composed of networks of regions that cooperate to perform specific cognitive
 35 operations (6-9). These functional networks show synchronized spontaneous activity while the
 36 brain is at rest, a phenomenon known as resting state functional connectivity (FC) (10-12). FC
 37 can be measured non-invasively in humans using resting-state functional MRI (rs-fMRI).
 38 Whole-brain rs-fMRI has been used to parse the brain into canonical functional networks (13,
 39 14), including visual, auditory and somatomotor networks (15, 16); ventral and dorsal attention
 40 networks (9, 17); a default mode network with roles in internally directed cognition and episodic
 41 memory (8, 12); a salience network thought to assess the homeostatic relevance of external
 42 stimuli (18); a frontoparietal control network supporting error-processing and moment-to-
 43 moment adjustments in behavior (1, 19, 20); and a cingulo-opercular control network (CON),
 44 which maintains executive control during goal-directed behavior (1, 19, 21).

45
 46 A more recent advance in human neuroscience has been the recognition of individual
 47 variability in network organization (22-25). Most early rs-fMRI studies examined central
 48 tendencies in network organization using group-averaged FC measurements (11, 13, 14).
 49 Recent work has demonstrated that functional networks can be described in an individual-
 50 specific manner if sufficient rs-fMRI data are acquired, an approach termed Precision
 51 Functional Mapping (PFM) (22, 23, 26-30). PFM respects the unique functional anatomy of
 52 each person and avoids averaging together functionally distinct brain regions across
 53 individuals.

54
 55 Somatomotor circuits do not function in isolation. Action selection and motor control are
 56 thought to be governed by complex interactions between the somatomotor network and control
 57 networks, including the CON (1). Here, we leveraged the whole-brain coverage of rs-fMRI and
 58 the statistical power of PFM to examine disuse-driven plasticity throughout the human brain.

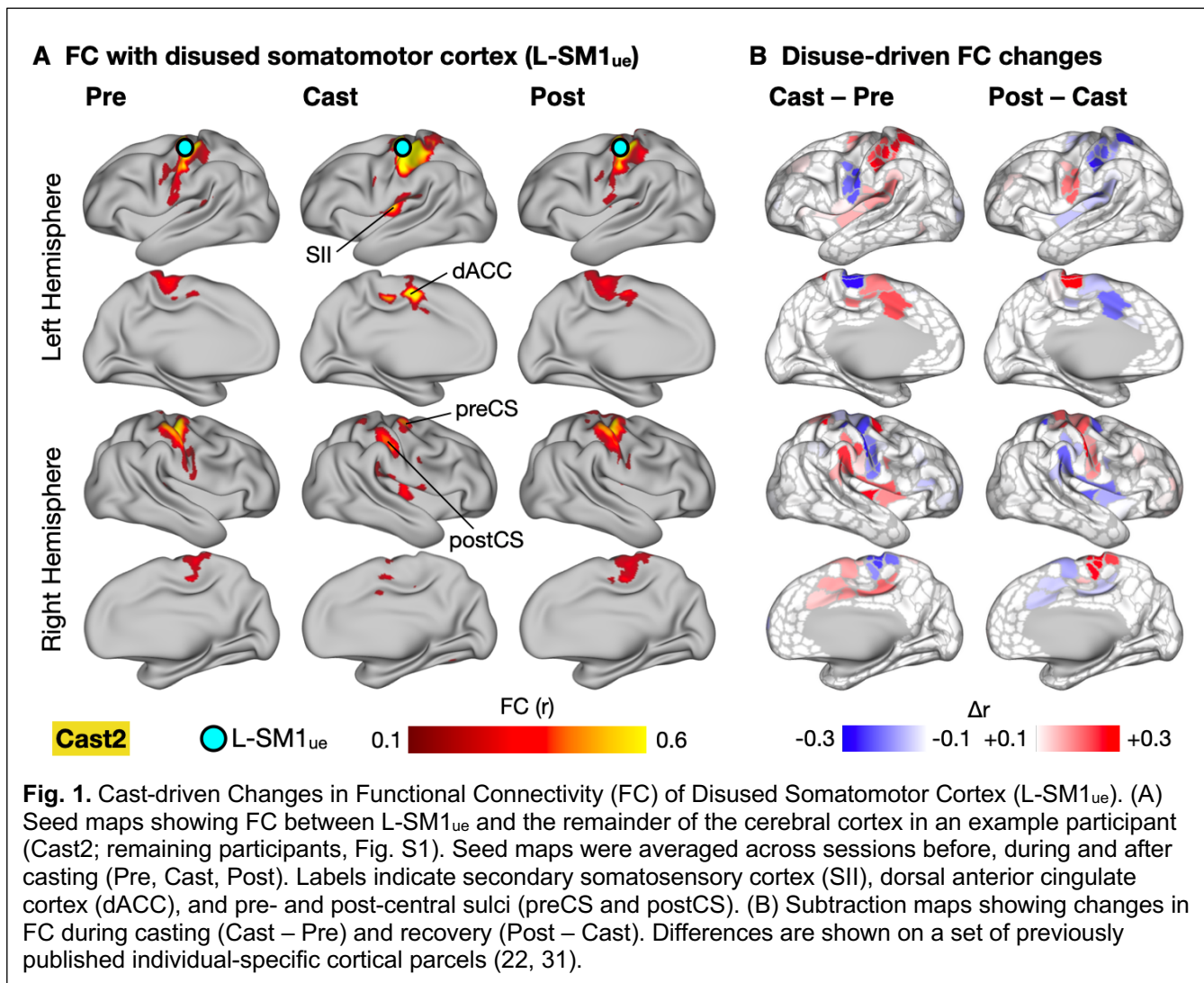
Results

Disuse Caused Both Increases and Decreases in Functional Connectivity

Three adult participants (“Cast1”, “Cast2” and “Cast3”) were scanned at the same time every day for 42-64 consecutive days (30 minutes of rs-fMRI/day) before, during and after two weeks of dominant upper extremity casting (31). To examine disuse-driven plasticity beyond somatomotor networks, we first generated seed maps showing FC between L-SM1_{ue} and all other cortical regions before, during and after casting (Fig. 1A, S1). Prior to casting (Pre), L-SM1_{ue} was strongly connected to the remainder of the somatomotor cortex (pre- and post-central gyri), especially homotopic R-SM1_{ue}. During the cast period (Cast), L-SM1_{ue} showed a new pattern of connectivity, with strong connections to bilateral secondary somatosensory cortex (SII), dorsal anterior cingulate cortex (dACC), and pre- and post-central sulci. After casting (Post), L-SM1_{ue} FC returned to baseline. Changes in FC during casting (Cast – Pre) and recovery (Post – Cast) were examined using sets of previously published individual-specific cortical parcels (22, 31). Casting caused decreased L-SM1_{ue} connectivity with the remainder of the somatomotor cortex, as well as increased connectivity with the bilateral SII, dACC, and pre- and post-central sulci (Fig. 1B, S1). FC changes after cast removal were strongly negatively correlated with changes during casting (Cast1: spatial correlation, $r = -0.56$, Cast2: $r = -0.95$, Cast3: $r = -0.32$; all participants: $P < 0.001$), indicating that most effects reversed after cast removal (Fig. 1B, S1).

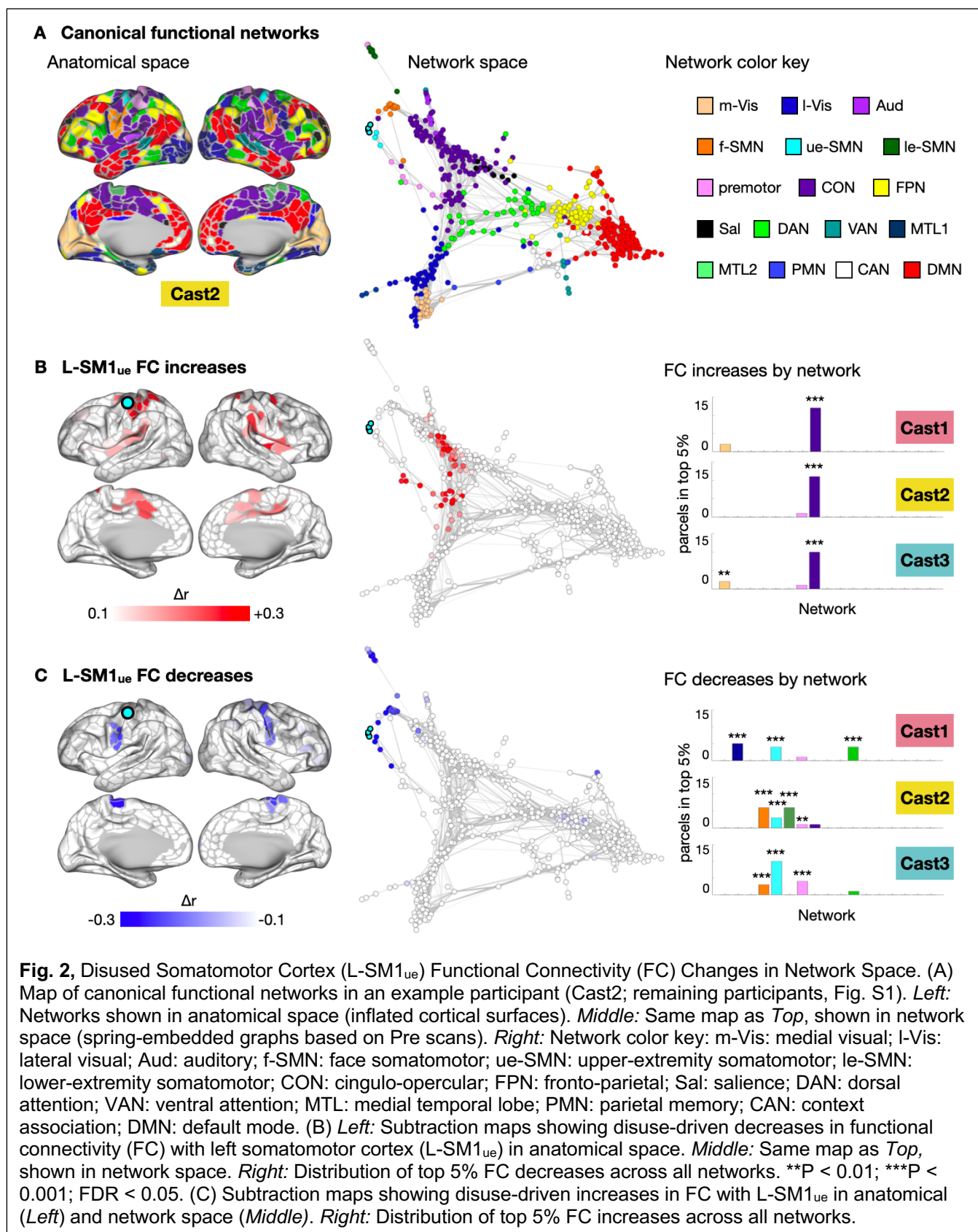
Disuse-driven Functional Connectivity Changes Were Highly Focal in Network Space

The brain’s functional network organization can be visualized using spring-embedded graphs, which treat functional connections as spring forces, positioning more strongly connected nodes closer to one another (Fig. 2A, S2). While L-SM1_{ue} FC increases were distributed in anatomical space, including regions on the medial and lateral surfaces of both hemispheres, nearly all of



these changes mapped onto a single cluster in network space, the CON (Fig. 2B, S2). The network focality of L-SM1_{ue} FC increases was quantified by examining the distribution of the greatest FC increases (top 5%) across the canonical functional networks (Fig. 2B). In all participants, the CON showed more FC increases than expected by chance ($P < 0.001$ for all participants). Decreases in L-SM1_{ue} FC were also localized in network space (Fig. 2C, S2). Most of the regions showing decreased FC with L-SM1_{ue} during casting belonged to the somatomotor networks (ue-SMN, le-SMN, face-SMN and premotor). All participants showed more FC decreases than expected by chance in the upper-extremity somatomotor network (ue-SMN; $P < 0.001$ for all participants). Additionally, two participants (Cast2 and Cast3)

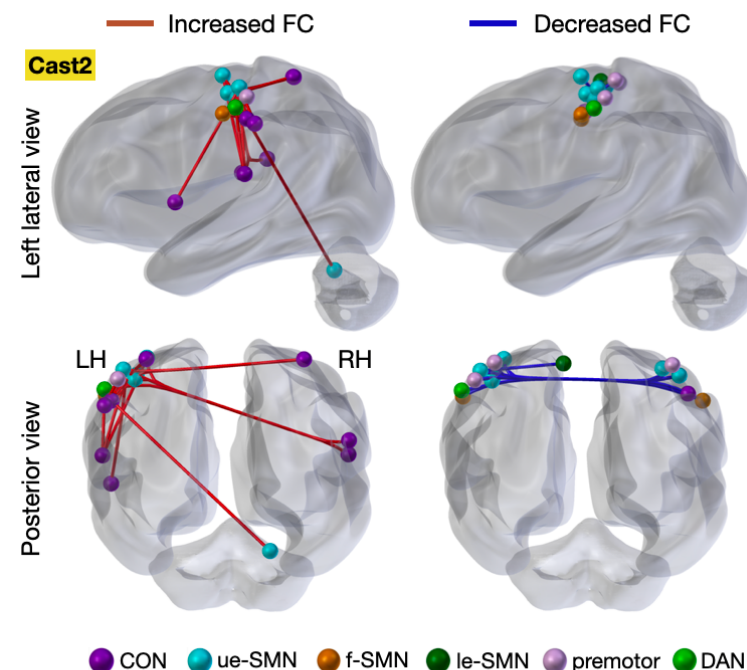
93 showed significant FC decreases in other somatomotor networks, including the lower-extremity
94 and face somatomotor networks (le-SMN and f-SMN) and the premotor network.



Plasticity Was Restricted to the Somatomotor and Cingulo-opercular Networks

The analyses presented thus far focus on changes in connectivity between L-SM1_{ue} and the remainder of the cerebral cortex. To examine whole-brain patterns of FC changes induced by casting, we extracted rs-fMRI signals from individual-specific cortical, subcortical and cerebellar parcels (Cast1: 744 parcels, Cast2: 733; Cast3: 761) and examined FC changes in all possible pairwise connections (Fig. S3). We displayed the 50 largest changes in FC (25 greatest increases and 25 greatest decreases) in anatomical space (Fig. 3A, S3). Disuse-driven FC changes involved L-SM1_{ue} more than expected by chance (Cast1: 9/50 connections, $P = 0.018$; Cast2: 37/50, $P < 0.001$; Cast3: 39/50, $P < 0.001$). Figure 3B shows the total

A Cast-induced FC changes between all brain regions



B Brain regions showing greatest FC changes

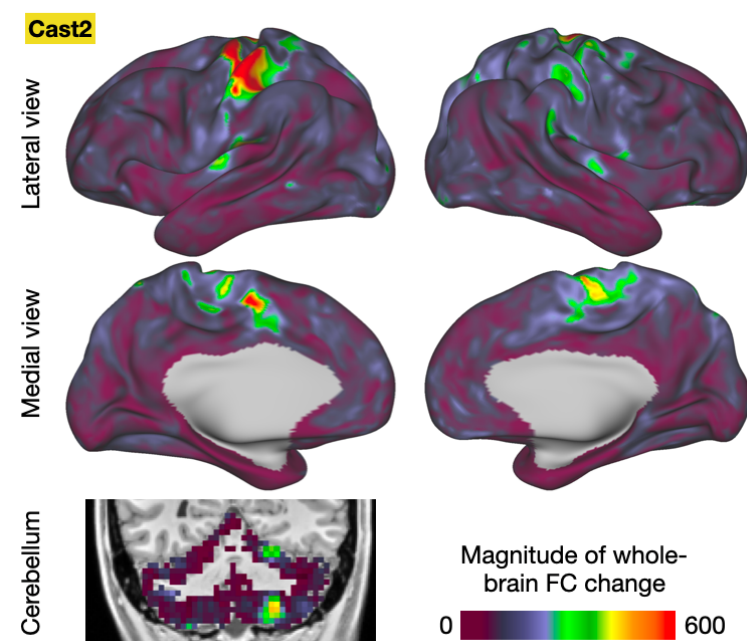


Fig. 3. Whole-brain Analyses of Disuse-driven Functional Connectivity (FC) Changes. (A) Changes in functional connectivity (FC) were computed for all pairs of cortical, subcortical and cerebellar parcels (mean Cast FC – mean Pre FC). The 50 most altered functional connections (top 25 increases, top 25 decreases) are shown for an example participant (Cast2; all participants, Fig. S3). (B) For each vertex/voxel, the magnitude of whole-brain FC change was computed as the sum of squared FC changes between that vertex and every other gray-matter vertex/voxel. Shown for an example participant (Cast2; all participants shown in Fig. S4).

magnitude of whole-brain FC change for each vertex/voxel. The total magnitude of whole-brain FC change was significantly greater in L-SM1_{ue} than in the remainder of the brain (Fig. 3B, S3; Cast1: $P = 0.021$; Cast2: $P < 0.001$; Cast3: $P = 0.005$).

Increased Connectivity with the CON Depended on a Recent History of Disuse

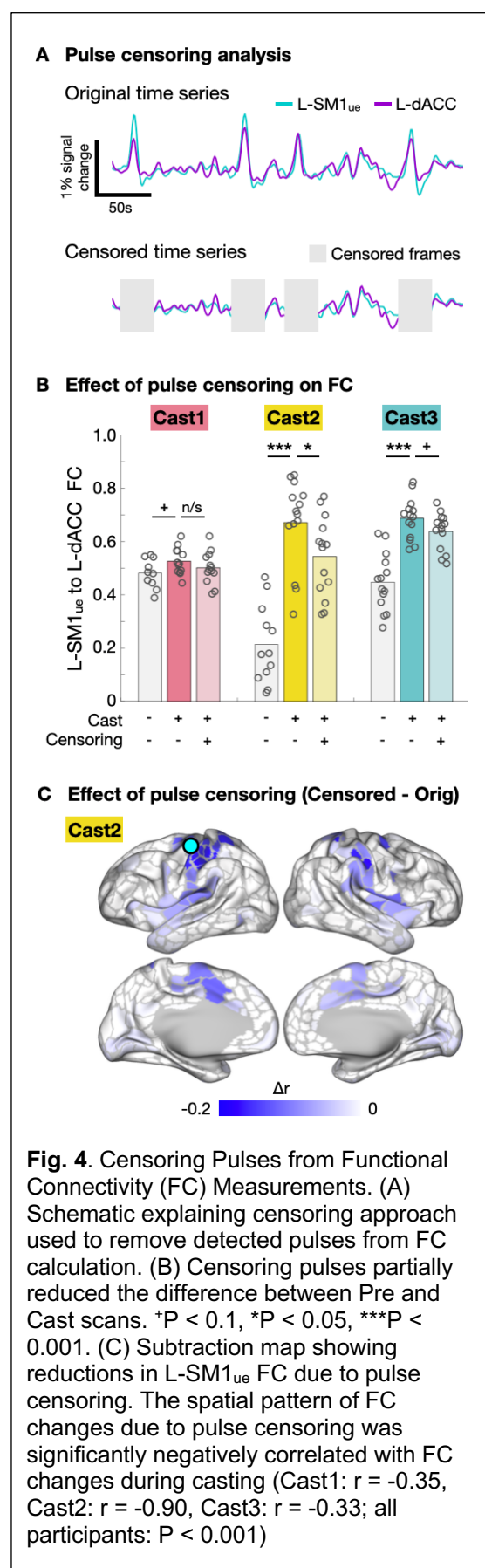
To distinguish between increases in connectivity due to wearing a cast during MRI scans (i.e., an altered behavioral state) and increases in connectivity due to a history of having been casted (i.e., disuse-driven plasticity), we conducted a control experiment in which participants wore casts during 30-minute scans but were not casted during their daily lives. In both cases, we compared FC between L-SM1_{ue} and the left dorsal anterior cingulate cortex (L-dACC; Fig. S4A), a key node of the CON, in cast and no-cast conditions. As suggested by the whole-brain network analyses (Fig. 2B), FC between L-SM1_{ue} and L-dACC was significantly increased during the cast period (Fig. S4B). When participants wore casts during scans, but were not casted during their daily lives, no changes in FC were observed (Fig. S4C). This control experiment indicated that increased FC between the disused motor circuitry and the CON depended on participants' recent history of disuse, not their current state of casting.

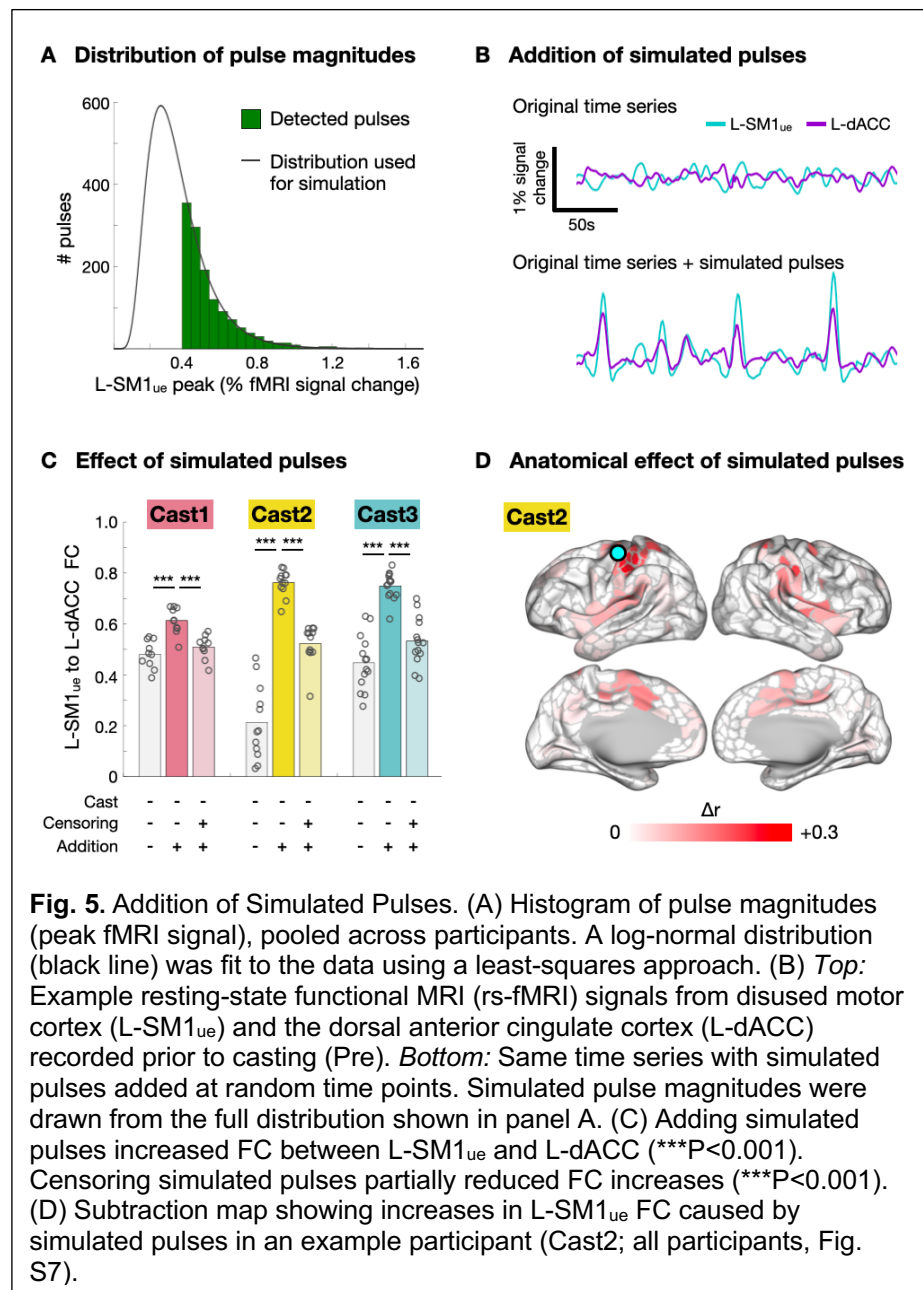
Network-Specific Connectivity Changes Reflect Spontaneous Activity Pulses

Increases in FC with L-SM1_{ue} showed a similar anatomical distribution to the spontaneous activity pulses we described previously (31) (Fig. S5A-B). Additionally, FC between L-SM1_{ue} and the CON was highly correlated with the number of pulses detected in L-SM1_{ue} during each scan (Fig. S5C; Cast1: $r=0.74$, Cast2: $r=0.57$, Cast3: $r=0.73$; all participants: $P<0.001$). These observations led us to suspect that FC between L-SM1_{ue} and the CON was increased during the cast period because both regions showed synchronized spontaneous activity pulses.

144

145 To test if spontaneous activity pulses could explain
 146 observed increases in FC, we implemented a pulse
 147 censoring strategy, in which frames surrounding
 148 each detected pulse (13.2 s before – 17.6 s after
 149 each pulse peak) were excluded from FC
 150 calculations (Fig. 4A). This approach is similar to the
 151 censoring strategy commonly used to correct the
 152 effects of head-motion on FC (32). Censoring pulses
 153 partially reduced the FC changes observed during
 154 casting (Fig. 4B; Cast1 -55%, $P = 0.14$; Cast2: -28%,
 155 $P = 0.02$; Cast3: -21%, $P = 0.04$; one-tailed t-test).
 156 Additionally, the spatial pattern of FC changes
 157 caused by pulse censoring (Censored – Uncensored;
 158 Fig. 4C, S6) was negatively correlated with FC
 159 changes during casting (Cast1: $r = -0.35$, Cast2: $r = -$
 160 0.90 , Cast3: $r = -0.33$; all participants: $P < 0.001$).
 161
 162 Censoring pulses did not entirely eliminate the effect
 163 of casting on FC. The residual effect of casting after
 164 pulse censoring was negatively spatially correlated
 165 with the effects of pulse censoring (Fig. S6; Cast1:
 166 spatial correlation, $r = -0.23$, Cast2: $r = -0.76$, Cast3:
 167 $r = -0.18$; all participants: $P < 0.001$), suggesting that
 168 the residual effect may have been driven by





SM1_{ue} and L-dACC after pulse censoring, we simulated a full distribution of pulse magnitudes by adding the mean pulse time series from L-SM1_{ue} and L-dACC to the baseline rs-fMRI signals recorded from these regions prior to casting (Fig. 5B). Simulated pulse magnitudes were drawn from a log-normal distribution, fit to the magnitude distribution of detected pulses using a least-squares approach (Fig. 5A; see S7 for triangular and exponential distributions). Adding simulated pulses caused FC increases with a similar effect size (Cast1: $\Delta r = +0.07$, $P = 0.013$; Cast2: $+0.40$, $P < 0.001$; Cast3: $+0.19$, $P < 0.001$) to the FC increases observed during

194 casting (Fig. 5C). Applying the same pulse censoring strategy described above to the
 195 simulated pulses partially reduced the increases in FC (Fig. 5C; Cast1: -79%, Cast2: -58%,
 196 Cast3: -69%; all participants: $P < 0.001$), similar to the effect of pulse censoring on the actual
 197 data (Fig. 4B). Adding simulated pulses to all brain regions, using mean pulse time series
 198 specific to each region, recreated the anatomical distribution of FC changes observed during
 199 casting (Fig. 5D, S8; Cast1: $r = 0.44$, Cast2: $r = 0.95$, Cast3: $r = 0.64$; all participants: $P <$
 200 0.001). Thus, pulse with a full distribution of magnitudes could account for observed FC
 201 changes during casting and the partial reversal of FC changes after pulse censoring.

202

203 We also utilized the pulse censoring and pulse addition analyses to test if pulses could explain
 204 observed decreases in FC within the somatomotor system. Pulse censoring did not
 205 significantly reverse the decrease in FC between L-SM1_{ue} and R-SM1_{ue} observed during the
 206 cast period (Fig. S9). Adding simulated pulses to baseline time series decreased FC between
 207 L-SM1_{ue} and R-SM1_{ue}, but this effect was much smaller than that observed during casting (Fig.
 208 S9).

209

210 Discussion

211 Disuse Drives Plasticity of Functional Networks

212 Daily 30-minute scans of rs-fMRI before, during, and after casting revealed that disuse not only
 213 causes plasticity within the primary motor cortex (4, 31), but also increased functional
 214 connectivity between disused circuits and executive control regions in the CON. These
 215 increases in FC would have been difficult to observe using the focal recording techniques
 216 traditionally employed to study plasticity. Thus, understanding the total impact of disuse on
 217 brain function requires consideration of plasticity at multiple spatial scales.

218

219 The high degree of network specificity seen in disuse-driven plasticity is a powerful
 220 demonstration of the validity of individual-specific rs-fMRI network parcellations. It could have
 221 been the case that casting produced a complex pattern of FC changes involving many brain
 222 systems. Instead, we found that virtually all of the regions showing increased connectivity with
 223 the disused motor cortex belonged to a single network, the CON. Thus, large-scale functional
 224 networks seem to be a fundamental unit of brain organization, important not only for
 225 understanding patterns of activation during cognitive processes, but also for understanding
 226 whole-brain patterns of plasticity.

227

228 **Spontaneous Activity Pulses Alter Functional Connectivity**

229 The network-specific increases in FC between the disused L-SM1_{ue} and the CON likely reflect
 230 the emergence of synchronized spontaneous activity pulses in these regions during casting.
 231 FC is a measurement of the temporal correlation of spontaneous activity between brain
 232 regions. Two complementary analyses (pulse censoring and pulse addition) suggested that
 233 pulses contributed to increases in measured FC between disused motor regions and the CON.
 234 Many studies have reported increased FC in neuropsychiatric conditions, e.g., Parkinson's
 235 disease (33) and Major Depressive Disorder (34). Perhaps some previously reported FC
 236 increases could reflect spontaneous activity pulses, similar to those caused by limb disuse.
 237 Going forward, spontaneous activity pulses, and the network-specific FC changes they
 238 produce, could serve as a biCast3ker of recent disuse and states of heightened plasticity (35).

239

240 Decreases in connectivity within the somatomotor system were not fully explained by
 241 spontaneous activity pulses. Although the pulse addition analyses showed that spontaneous
 242 activity pulses could contribute to decreases in connectivity observed during casting, both the
 243 pulse censoring and pulse addition analyses suggested that at least part of the observed

decrease in connectivity occurred independently of pulses. Loss of typical co-activation of L-SM_{1ue} and R-SM_{1ue} during daily behavior (31) likely contributed to cast-driven connectivity decreases, consistent with the widely held hypothesis that FC is maintained by a Hebbian-like mechanism that depends on co-activation of brain regions during behavior (19, 36-39).

Disuse Impacts Cingulo-opercular Network (CON) Important for Executive Control

The importance of control systems in the human brain has been recognized for several decades (7), but our understanding of these systems has changed dramatically over time and continues to evolve (40). Disentangling the roles of two networks mediating executive control, the cingulo-opercular and frontoparietal networks, has relied largely on complex task designs such as task-switching (21) and slow-reveal paradigms (41). Here, we have demonstrated that a new approach, whole-brain precision functional mapping combined with anatomically specific disuse paradigms, can shed new light on the network interactions that support human cognition and behavior. Although the brain contains several suspected control networks beyond the CON, such as the frontoparietal (FPN), dorsal attention (DAN), ventral attention (VAN) and salience (SAL) networks, disused motor regions showed increased FC only with the CON. The CON is thought to initiate goal-directed behaviors and maintain executive control settings in relation to task objectives (1, 19). The increased FC between disused L-SM_{1ue} and the CON during casting suggests either 1) circuits within the CON were also disused during casting, 2) the CON helps to maintain disused motor circuitry, or 3) spontaneous activity pulses can spread along functional connections to neighboring brain regions in network space.

Spontaneous activity pulses may have emerged in the CON because its use was also reduced during casting. We previously suggested that spontaneous activity pulses found in motor regions may have been caused by disuse-driven changes in local inhibitory physiology (31,

269 42). The CON is generally thought to represent task sets, abstract parameters and motor
 270 programs governing goal-driven behaviors (1, 19). Task sets can be applied to multiple motor
 271 effectors (e.g., right hand, left index finger, etc.), so it would be reasonable to think that casting
 272 one extremity would not cause disuse of the CON. However, at least two sets of circuits within
 273 the CON may have been disused during casting: circuits that represent bimanual behaviors
 274 and circuits that convey task sets to effector-specific downstream regions (e.g., L-SM1_{ue}).
 275 During casting, many of the task sets previously used to control the dominant upper extremity
 276 (e.g., inserting a key into a lock) could have been used to control the non-dominant extremity.
 277 However, task sets requiring bimanual coordination (e.g., fastening a belt) could not be applied
 278 to an alternative set of motor effectors and may have become disused. Another set of CON
 279 circuits that may have been disused are the circuits that convey task set information to
 280 effector-specific brain regions. The CON contains both somatotopically organized regions
 281 (e.g., SMA, SII) and non-somatotopic regions (e.g., anterior insula). Recent work shows that
 282 the SMA and SII, as well as regions of the basal ganglia, may act as hubs that connect the rest
 283 of the CON to the somatomotor network (27, 43). Such circuits could potentially undergo
 284 disuse during casting of one extremity.

285

286 An alternative possibility is that inputs from the CON to L-SM1_{ue} served a homeostatic function
 287 during disuse, helping to maintain motor circuits that are typically maintained through active
 288 use. We previously suggested that spontaneous activity pulses may help to maintain the
 289 organization of disused brain circuits (31). Perhaps pulses are triggered by the CON, which is
 290 the system typically responsible for initiating activation of the somatomotor network (1).

291

292 Spontaneous activity pulses may also have originated in the disused somatomotor circuits and
 293 spread along functional connections to brain regions that were not affected by casting. The

294 CON is immediately adjacent to the somatomotor network in network space (Fig. 2A). Previous
 295 work in mice found that spontaneous activity bursts in somatosensory cortex, caused by local
 296 pharmacogenetic suppression of inhibitory interneurons, spread to other functionally
 297 connected regions not targeted by the experimental manipulation (44). An interesting question
 298 for future research is whether the CON would show spontaneous activity pulses following
 299 disuse of brain systems other than the somatomotor network, such as networks supporting
 300 visual and auditory processing, spatial navigation, or social cognition.

301

302 **Two Complementary Mechanisms for Functional Network Plasticity**

303 Extensive whole-brain imaging before, during and after casting revealed that disuse-driven
 304 spontaneous activity pulses occur not only in primary motor and somatosensory areas, but
 305 also in higher-order brain regions responsible for executive control over behavior. The
 306 emergence of spontaneous activity pulses during casting produced increases in FC that were
 307 highly focal in network space, specifically occurring between disused motor regions and the
 308 CON. Decreases in connectivity between disused motor circuits and the remainder of the
 309 somatomotor system, however, were not explained by spontaneous activity pulses. Thus,
 310 disuse may drive network plasticity through two complementary mechanisms. Decreased
 311 coactivation of brain regions during disuse might drive Hebbian-like disconnection between
 312 disused and still-active somatomotor circuits. Spontaneous activity pulses, which contributed to
 313 increased connectivity with the CON, may help preserve disused circuits for future
 314 reintegration and use. Together, these two network plasticity mechanisms—Hebbian-like and
 315 pulse-mediated—may represent a network-focal “stand-by mode” that allows the brain to
 316 isolate disused circuits while simultaneously protecting them from premature functional
 317 degradation.

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Author Contributions:

D.J.N., T.O.L., C.R.H., A.Z.S., and N.U.F.D. designed the study. D.J.N., C.R.H., J.M.H., M.O., and N.U.F.D. collected the data. D.J.N. and E.M.G. analyzed the data. D.J.N., E.M.G., T.O.L., N.A.S., D.F.M., S.J.G., A.Z., A.N.N., B.A., A.R.C., B.P.K., D.J.G., M.E.R., S.E.P., A.Z.S., and N.U.F.D. interpreted the results. D.J.N. and N.U.F.D. wrote the manuscript with input from all other authors.

Declaration of interests:

The authors declare the following competing financial interest: N.U.F.D. is co-founder of NOUS Imaging.

METHODS

318 ***Human Participants***

319 Participants were three healthy, adult volunteers. Details are described in Newbold *et al.* (31).

320 ***Experimental Intervention***

321 We constrained the dominant upper extremity for two weeks by fitting each participant with a fiberglass
322 cast. Casts extended from just below the shoulder to past the fingertips. Details are described in
323 Newbold *et al.* (31).

324 ***MRI Acquisition***

325 Participants were scanned every day of the experiment for 42-64 consecutive days. We collected 30
326 minutes of resting-state functional MRI (rs-fMRI) data every day of the experiment, as well as also task
327 fMRI and T1- and T2-weighted structural scans. Acquisition parameters and procedures are detailed in
328 Newbold *et al.* (31).

329 ***MR Image Processing***

330 Preprocessing of structural and functional images, denoising of resting-state fMRI data, and cortical
331 surface projection were performed previously (31). Fully processed data are available in the Derivatives
332 folder of the Cast-Induced Plasticity dataset on OpenNeuro (www.openneuro.org/datasets/ds002766).

333 ***ROI Selection***

334 The region of the left primary somatomotor cortex controlling the casted upper extremity (L-SM1_{ue}) was
335 located individually in each participant using task fMRI. Details of the task analysis and region of
336 interest (ROI) selection are described in Newbold *et al.* (31). The L-SM1_{ue} ROI was used here to
337 generate seed maps (Fig. 1, S1), to analyze spatial specificity of whole-brain functional connectivity
338 changes (Fig. 3B, S3) and to measure FC between L-SM1_{ue} and the dorsal anterior cingulate cortex
339 (dACC) for the removable cast control experiment (Fig. S4), the pulse censoring analysis (Fig. 4) and
340 the pulse addition analysis (Fig. 5, S7).

341 Individual-specific sets of parcels spanning the entire cerebral cortex were previously generated for
 342 each participant using a functional connectivity gradient-based approach, and each parcel was
 343 assigned to one of 17 canonical functional networks using a graph theory-based community detection
 344 algorithm (22, 31). Cortical parcels were used here to display functional connectivity changes in
 345 anatomical (Fig. 1-2, 5, S1-S2, S4-S6) and network space (Fig. 2, S2). We also generated a set of
 346 subcortical and cerebellar parcels by assigning each voxel to the functional network with which it
 347 showed the strongest functional connectivity and then grouping adjacent voxels with matching network
 348 assignments into parcels. Sets of cortical, subcortical and cerebellar parcels were used to examine
 349 changes in FC between all pairs of brain regions (Fig. 3, S2).

350 A subset of parcels corresponding to the left primary somatomotor cortex (L-SM1_{ue}) was previously
 351 generated by selecting all left-hemisphere parcels assigned to the upper-extremity somatomotor
 352 network, excluding any parcels that fell outside of the pre- and post-central gyri (31). Functional
 353 connections between L-SM1_{ue} parcels and all other parcels were averaged to generate parcel-wise
 354 seed maps (Fig. 1-2, 5, S1-S2, S4-S6) and to quantify the spatial specificity of FC changes between all
 355 cortical, subcortical and cerebellar parcels (Fig. 3, S3).

356 Individual-specific ROIs in the left dorsal anterior cingulate cortex (L-dACC) were selected using pulse
 357 analysis of variance (ANOVA) maps, which were previously generated for each participant (31). ROIs
 358 were selected within a large anatomical region, automatically labeled by FreeSurfer (union of caudal
 359 anterior cingulate gyrus, posterior cingulate gyrus, and superior frontal gyrus). We first located the
 360 vertex showing the maximum ANOVA F-statistic and then iteratively expanded the ROI by selecting
 361 neighboring vertices in descending order of F-statistic, until the ROI included 100 vertices. The L-dACC
 362 ROI was used to measure FC between L-SM1_{ue} and the L-dACC for pulse censoring (Fig. 4) and pulse
 363 addition analyses (Fig. 5, S7).

364 **Functional Connectivity Measurement**

365 Mean rs-fMRI time series were extracted from the L-SM1_{ue} ROI and each cortical, subcortical and
 366 cerebellar parcel by averaging the time series of all vertices/voxels within the ROI/parcel. Vertex-wise
 367 functional connectivity (FC) seed maps were generated for each session by computing a Pearson
 368 correlation between the mean rs-fMRI time series from the L-SM1_{ue} ROI and the time series from every
 369 vertex. Frames with high head motion, identified previously (31), were excluded from FC calculations.
 370 Vertex-wise seed maps were averaged across sessions before, during and after casting (Pre, Cast,
 371 Post; Fig. 1, S1).

372 FC between all pairs of cortical, subcortical and cerebellar parcels was measured as pairwise
 373 correlations of all mean rs-fMRI time series, excluding high-motion frames, producing a correlation
 374 matrix for each session. Correlation matrices were averaged over Pre, Cast and Post period. FC
 375 changes during casting and recovery were computed as the differences between correlation matrices
 376 (casting = Cast – Pre; recovery = Post – Cast). Full Cast – Pre differences matrices are shown in
 377 Figure S3. Parcel-wise difference seed maps showing changes in L-SM1_{ue} FC during casting and
 378 recovery (Fig. 1-2, S1-S2) were computed by averaging together columns of the difference matrices
 379 corresponding to the L-SM1_{ue} parcels (see *ROI selection*, above).

380 **Spring Embedding**

381 Cortical parcels were displayed in network space using force-directed (“spring-embedded”) graphs(45),
 382 generated with Gephi (<https://gephi.org/>). Graph weights were taken from parcel-wise correlation
 383 matrices averaged across all sessions prior to casting (Pre). Graphs were thresholded to include only
 384 the top 0.2% of pairwise functional connections. We initially examined graphs using an edge threshold
 385 of 0.1%, but several parcels with large FC changes were disconnected from the main graph. Thus, we
 386 selected the 0.2% connection threshold to display all key findings (Fig. 2, S2).

387 **Functional Connectivity Changes by Network**

388 To test which functional networks showed large changes in FC with L-SM1_{ue} during casting, parcel-wise
 389 L-SM1_{ue} seed maps were compared to individual-specific network maps. Parcel-wise L-SM1_{ue}
 390 difference seed maps (Cast – Pre) were thresholded to contain the top 5% of parcels showing FC
 391 increases/decreases. FC increases (Cast > Pre) and decreases (Cast < Pre) were examined
 392 separately. The number of supra-threshold parcels in each cortical network is shown in Figure 2.
 393 Alternative thresholds (top 1%, 10% and 20%) all yielded similar results. Networks containing a greater
 394 number of FC increases/decreases than expected by chance were identified by comparing the number
 395 of supra-threshold parcels found using each participant's true network map to the number of parcels
 396 found using spatially permuted network maps (see *Statistical analyses*, below).

397 **Whole-brain Analyses of Functional Connectivity Changes**

398 The spatial specificity of whole-brain plasticity was examined by comparing changes in FC between all
 399 cortical, subcortical and cerebellar parcels to individual-specific functional network maps. We examined
 400 the top 50 changes in FC (25 greatest increases and 25 greatest decreases). A change in FC between
 401 two parcels was counted as involving L-SM1_{ue} if either of the two parcels was an L-SM1_{ue} parcel. The
 402 number L-SM1_{ue} changes found using each participant's true network map was compared to the
 403 number of L-SM1_{ue} changes found using spatially permuted network maps (see *Statistical analyses*,
 404 below).

405 To examine whole-brain FC changes at a finer spatial resolution, we examined differences in FC
 406 between all cortical, subcortical and cerebellar vertices/voxels. We computed the magnitude of whole-
 407 brain FC change between each vertex/voxel as the sum of squared FC changes between that
 408 vertex/voxel and every other gray-matter vertex/voxel (Fig. 3, S3). We tested if whole-brain FC change
 409 was higher in L-SM1_{ue} than in the rest of the brain by comparing the mean magnitude of whole-brain
 410 FC change inside of each participant's true L-SM1_{ue} ROI to the mean magnitude of whole-brain FC
 411 change inside of spatially rotated ROIs (see *Statistical analyses*, below).

Spatial and Temporal Comparisons of Pulses and FC Changes

To generate a parcel-wise map of spontaneous activity pulses, we extracted rs-fMRI time series from every cortical, subcortical and cerebellar parcel surrounding each detected pulse (13.2 seconds before to 17.6 seconds after each pulse peak). Pulse peaks were detected previously (31). We then performed an ANOVA on the extracted time series (Fig. S5B). The spatial distribution of ANOVA F-statistics was compared to the spatial distribution of L-SM1_{ue} FC changes using a Pearson correlation across parcels. We also compared the number of pulses detected during each rs-fMRI scan (31) to the FC measured between L-SM1_{ue} and L-dACC (Fig. S4C), using a Pearson correlation.

Pulse Censoring Analyses

To assess the contribution of large, detectable spontaneous activity pulses (>0.4% rs-fMRI signal change) to FC changes observed during casting, frames surrounding each pulse (13.2 seconds before to 17.6 seconds after each pulse peak) were excluded from FC calculations. Pulse detection criteria were identical to those used previously (31). We plotted FC measured between L-SM1_{ue} and L-dACC during each session before casting (Pre), during casting (Cast) and during casting with pulses excluded (Cens; Fig. 4B). We compared Cast vs. Pre FC measurements and Cens vs. Cast FC measurements using t-tests (see *Statistical analyses*, below). We also generated difference seed maps showing FC changes between L-SM1_{ue} and all cortical parcels due to censoring (Cens – Cast; Fig. 4C, S6).

Pulse Addition Analyses

To assess the contribution to FC changes of pulses with a hypothetical full magnitude distribution, including pulses that were too small (<0.4% rs-fMRI signal change) to distinguish from ongoing spontaneous activity fluctuations, we created simulated rs-fMRI time series containing a full distribution of pulses. We first generated a histogram showing the magnitude distribution of detected pulses. Magnitudes were grouped into bins with a width of 0.5%-signal-change. We then fit a log-normal distribution to the observed pulse magnitudes using a least-squares approach (Fig. 5A). This provided an estimate of the full pulse magnitude distribution, including pulses that were too small to detect. We

then added the mean pulse time series to the baseline (Pre) rs-fMRI time series, drawing pulse magnitudes from the full log-normal distribution (example shown in Fig. 5B). The number of pulses added was selected so that the number of large pulses (>0.4% signal change) would match the number of pulses detected in each participant in an average Cast scan. We then computed FC of the baseline time series (Pre) and the time series with added pulses (Sim; Fig. 5C). Finally, we applied the same pulse censoring strategy described above to the simulated time series and computed FC after censoring (Cens; Fig. 5C). Because pulse magnitudes were drawn from a full log-normal distribution, only a portion of the added pulses were detected and censored. We compared Sim vs. Pre FC measurements and Cens vs. Sim FC measurements using t-tests (see *Statistical analyses*, below). The simulation and censoring procedures were repeated using triangular and exponential magnitude distributions (Fig. S7). We also generated difference seed maps showing FC changes between L-SM1_{ue} and all cortical parcels due to pulse simulation (Sim – Pre; Fig. 5D, S8).

Statistical Analyses

All statistical tests were performed identically for each participant. Whenever appropriate, we used simple parametric statistical tests:

- Spatial similarity between anatomical maps was tested using a Pearson correlation across parcels (Cast1: d.f. = 566; Cast2: 578; Cast3: 624). Spatial correlations were computed between the following maps:
 - FC changes during casting (Cast – Pre) vs. FC changes during recovery (Post – Cast; Fig. 1B)
 - FC changes during casting (Cast – Pre) vs. pulse ANOVA (F-statistic; Fig. S5)
 - FC changes during casting (Cast – Pre) vs. FC changes due to pulse censoring (Cens – Cast; Fig. 4C, S6)
 - FC changes due to pulse censoring (Cens – Cast) vs. residual FC changes after pulse censoring (Cens – Pre; Fig. S6)

- FC changes during casting (Cast – Pre) vs. FC changes due to simulated pulses (Sim – Pre; Fig. 5D, S8)

- The number of pulses detected during each scan was compared to the FC measured between L-SM1_{ue} and L-dACC using a Pearson correlation (Cast1: d.f. = 45; Cast2: 61; Cast3: 40; Fig. S5C).
- FC between L-SM1_{ue} and L-dACC measured during each session of the cast period (Cast1: n = 13 sessions; Cast2: 13; Cast3: 14) was compared to FC during each session of the pre period (Cast1: n = 10; Cast2: 12; Cast3: 14) using a two-sided, unpaired t-test (Cast1: d.f. = 21, Cast2: 23, Cast3: 26; Fig. S5B).
- FC between L-SM1_{ue} and L-dACC measured using the full time series (motion-censored only) of each session of the cast period (Cast1: n = 13 sessions; Cast2: 13; Cast3: 14) was compared to FC measurements of the same sessions excluding pulses (motion- and pulse-censored) using a one-sided, paired t-test (Cast1: d.f. = 24, Cast2: 24, Cast3: 26; Fig. 4B).
- FC between L-SM1_{ue} and L-dACC measured during each session of the pre period (Pre; Cast1: n = 10; Cast2: 12; Cast3: 14) was compared to FC measurements of the same sessions after adding simulated pulses (Sim) using a two-sided, paired t-test (Cast1: d.f. = 18, Cast2: 22, Cast3: 26; Fig. 5C).
- FC between L-SM1_{ue} and L-dACC measured using the full time simulated series (Sim; motion-censored only; Cast1: n = 10; Cast2: 12; Cast3: 14) was compared to FC measurements of the same sessions excluding pulses (motion- and pulse-censored) using a two-sided, paired t-test (Cast1: d.f. = 18, Cast2: 22, Cast3: 26; Fig. 5C).

When parametric statistical tests were not appropriate to test a specific hypothesis, we tested results against a null distribution generated via permutation resampling. In each case, our null hypothesis was that observed effects had no spatial relationship to ROIs/functional networks and any overlap occurred by chance. For vertex-wise ROIs, we modeled the null hypothesis by rotating the ROI around the cortical surface 1,000 times (46, 47). For functional networks, we modeled the null hypothesis by

488 permuting the network assignments of parcels 1,000 times. Each permuted ROI/network map was used
 489 exactly as the actual map in order to compute a null distribution for the value of interest. The P-value
 490 reported for each test represents the two-sided probability that a value in the null distribution has a
 491 greater magnitude than the observed value. Permutation resampling was used to generate null
 492 distributions for the following values:

- 493 • Overlap of each functional network with increases in L-SM1_{ue} FC during casting (Cast > Pre;
 494 number of parcels in top 5%; Fig. 2B)
- 495 • Overlap of each functional network with decreases in L-SM1_{ue} FC during casting (Cast > Pre;
 496 number of parcels in top 5%; Fig. 2C)
- 497 • Overlap of L-SM1_{ue} parcels with the 50 largest changes in FC between all pairs of cortical,
 498 subcortical and cerebellar parcels (Fig. 3A, Fig. S3)
- 499 • Magnitude of whole-brain FC change in the L-SM1_{ue} ROI (Fig. 3B, S3)

500 Since we tested the overlap of L-SM1_{ue} FC increases/decreases with 17 different functional networks, a
 501 Benjamini-Hochberg procedure was applied to correct for multiple comparisons, maintaining false
 502 discovery rates < 0.05. Each of the three participants constituted a separate replication of the
 503 experiment, rather than multiple comparisons, so no correction was necessary for tests repeated in
 504 each participant.

505 ***Data Visualization***

506 Regions of interest and whole-brain pulse maps were shown on cortical surfaces generated by
 507 FreeSurfer (48) and Human Connectome Project (HCP) Workbench software packages (49). These
 508 images were rendered using HCP Workbench (49). Figures showing the greatest differences in
 509 functional connectivity across the entire brain in inflated anatomical space (Fig. 3, S3) were rendered
 510 using Blender, a free and open-source 3D modeling software package (www.blender.org). To make the
 511 large number of changed connections included in these images visually compact, connections following

512 similar spatial trajectories were drawn toward each other using a previously published mean-shift edge
513 bundling algorithm (50). All other figures were produced using Matlab (www.mathworks.com).

514 ***Data Availability***

515 This study used our previously published dataset (31), available on the OpenNeuro database
516 (www.openneuro.org/datasets/ds002766).

517 ***Code Availability***

518 All code needed to reproduce our analyses is available on Gitlab
519 (<https://gitlab.com/DosenbachGreene/cast-whole-brain>).

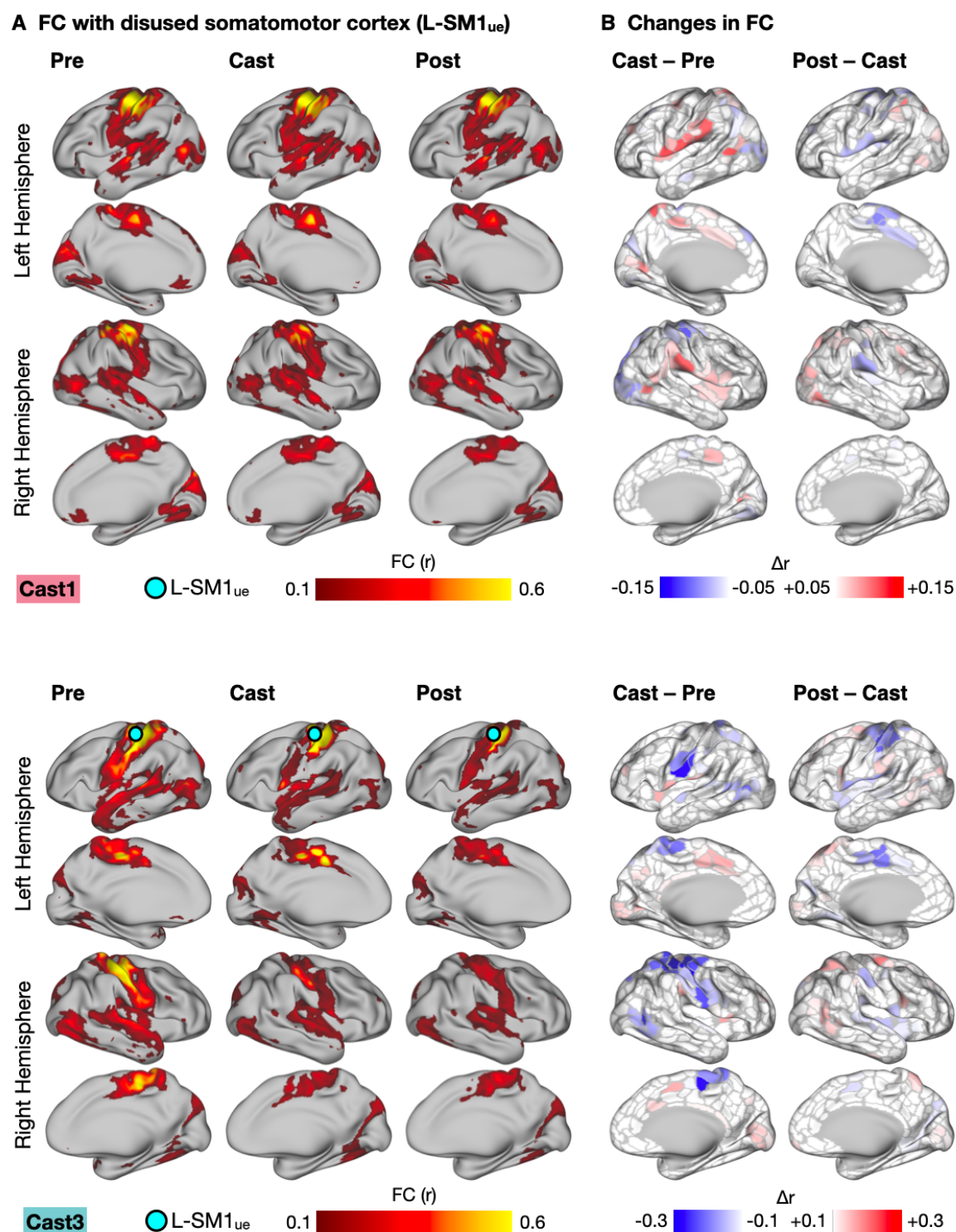


Fig. S1. Functional Connectivity (FC) Changes Involving the Disused Somatomotor Cortex (L-SM1_{ue}) in Anatomical Space (All Participants). (A) Seed maps showing FC between L-SM1_{ue} and the remainder of the cerebral cortex in Cast1 (top) and Cast3 (bottom). Seed maps were averaged across sessions before, during and after casting (Pre, Cast, Post). (B) Subtraction maps showing changes in FC during casting (Cast – Pre) and recovery (Post – Cast). Differences are shown on sets of 506 (Cast1) and 626 (Cast3) individual-specific cortical parcels. For Cast1 and Cast2, these parcels were previously generated and published (Gordon, 2017). We applied identical methods to generate a set of parcels for Cast3.

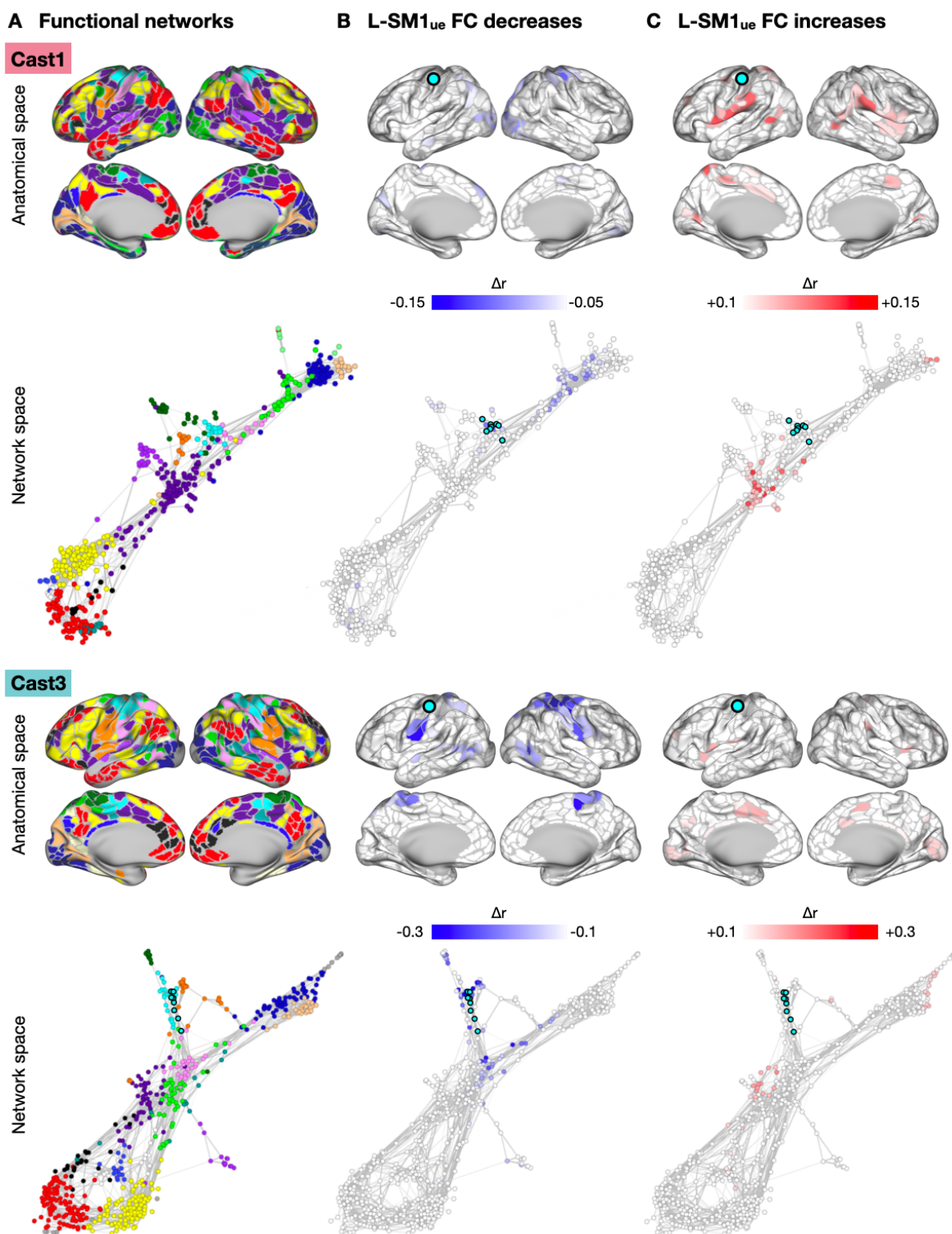
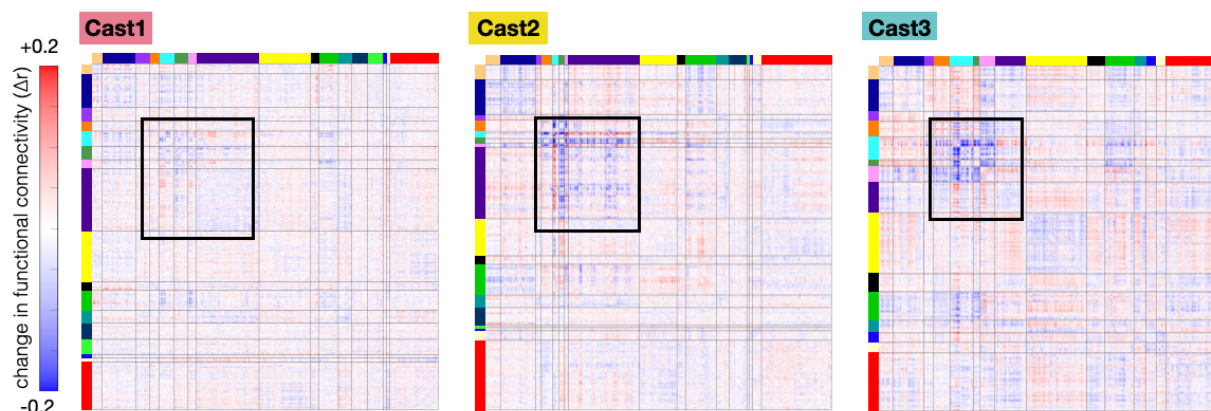
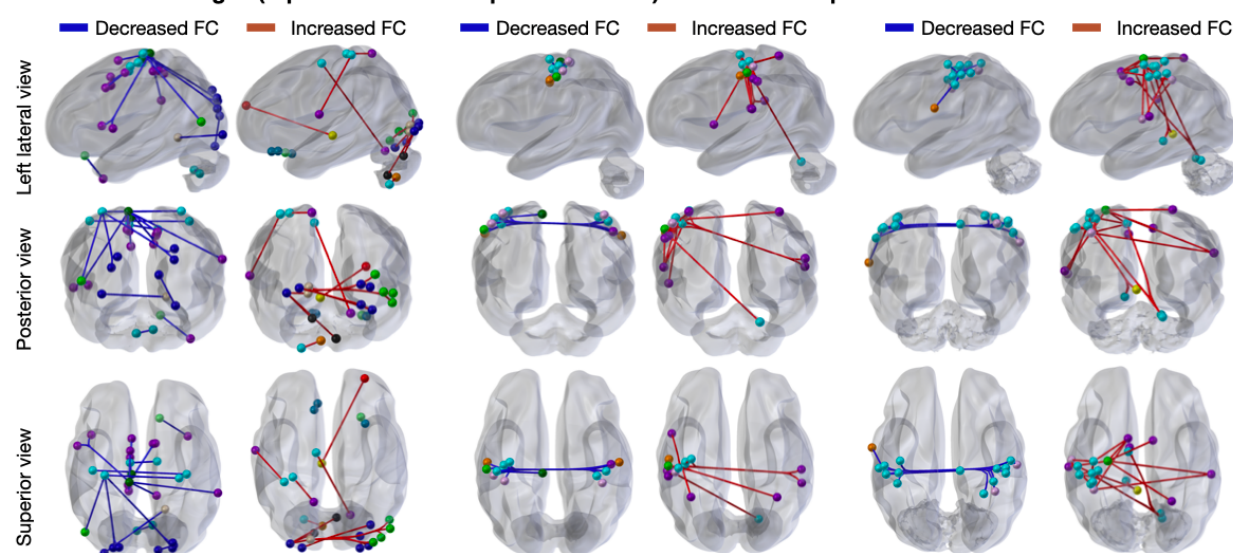


Fig. S2. Functional Connectivity (FC) Changes Involving the Disused Somatomotor Cortex (L-SM1_{ue}) in Anatomical and Network Space in Cast1 and Cast3. (A) Maps of 17 canonical functional networks in Cast1 (top) and Cast3 (bottom). Networks are shown in anatomical space (inflated cortical surfaces) and network space (spring-embedded graphs based on Pre scans). See Figure 2 for network color key. (B) Subtraction maps showing disuse-driven decreases in functional connectivity (FC) with left somatomotor cortex (L-SM1_{ue}) in anatomical space and network space. (C) Subtraction maps showing disuse-driven increases in FC with L-SM1_{ue} in anatomical and network space.

A Difference correlation matrices (Cast – Pre)



B Greatest FC changes (top 25 increases + top 25 decreases) in anatomical space



C Regions showing greatest FC changes

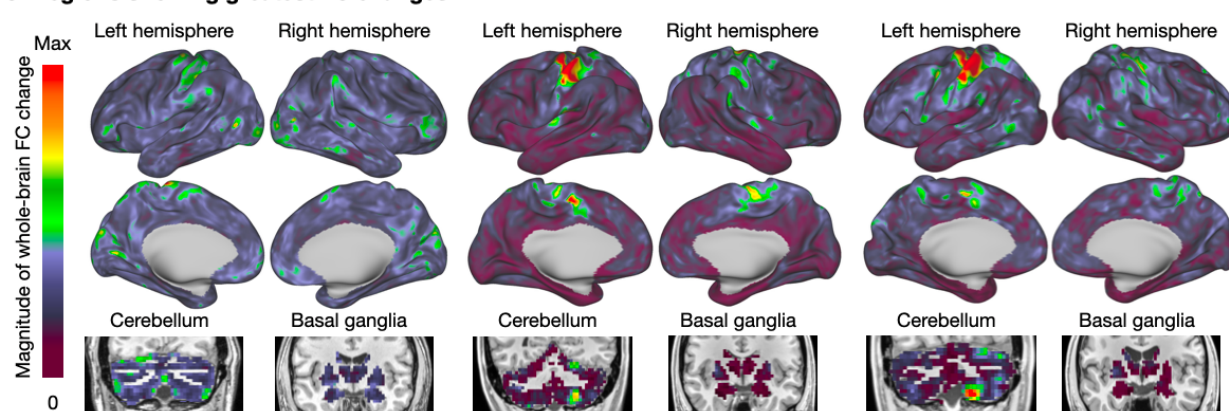
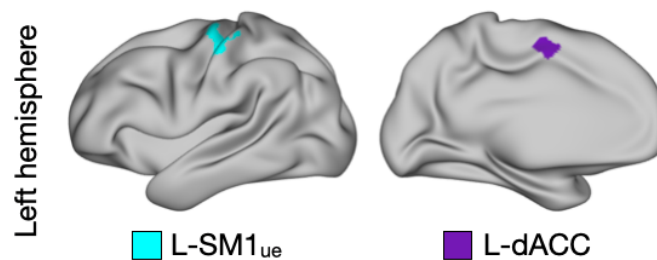
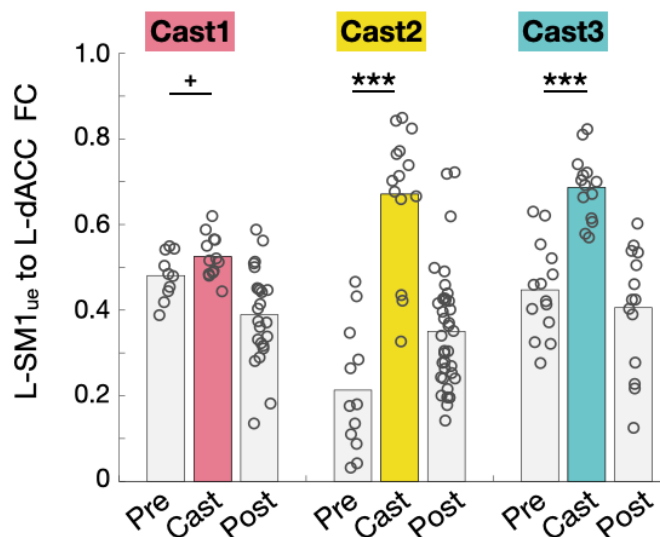


Fig. S3. Whole-brain Patterns of Disuse-driven Plasticity. (A) Matrices showing changes in functional connectivity (FC) between all pairs of individual specific cortical, subcortical and cerebellar parcels during casting (Cast1: 744 parcels, Cast2: 733; Cast3: 761). (B) 50 largest changes in FC shown in anatomical space. (C) Magnitude of whole-brain FC change, computed as the sum of squared FC changes between each vertex/voxel and every other gray-matter vertex/voxel.

A Motor and CON regions of interest



B Effect of disuse



C Effect of casting during scans

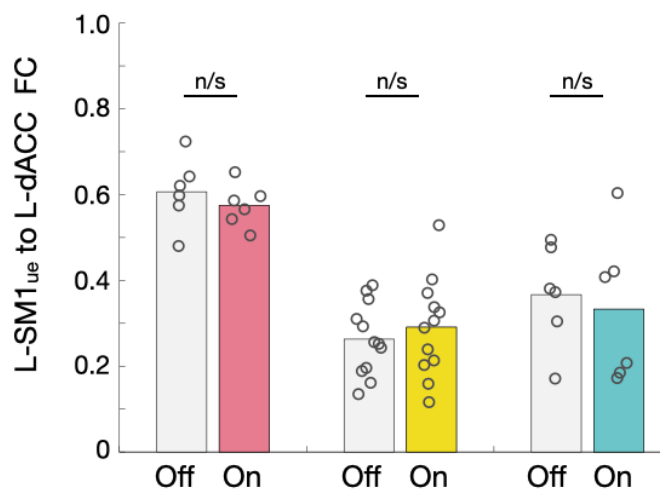


Fig. S4. Connectivity between Disused Somatomotor Cortex and Cingulo-opercular Network during Disuse and Temporary Casting. (A) Example regions of interest (ROIs) in the left primary somatomotor cortex (L-SM1_{ue}) and the left dorsal anterior cingulate cortex (L-dACC). (B) Functional connectivity (FC) measured between L-SM1_{ue} and L-dACC before (Pre), during (Cast) and after casting (Post). Two participants (Cast2 and Cast3) show a significant increase in FC during the cast period *P < 0.1, *P < 0.05, ***P < 0.001. (C) FC measured between L-SM1_{ue} and L-dACC during both conditions of the control experiment: without casting (Off) and with temporary casts during scans (On). No changes in FC were observed.

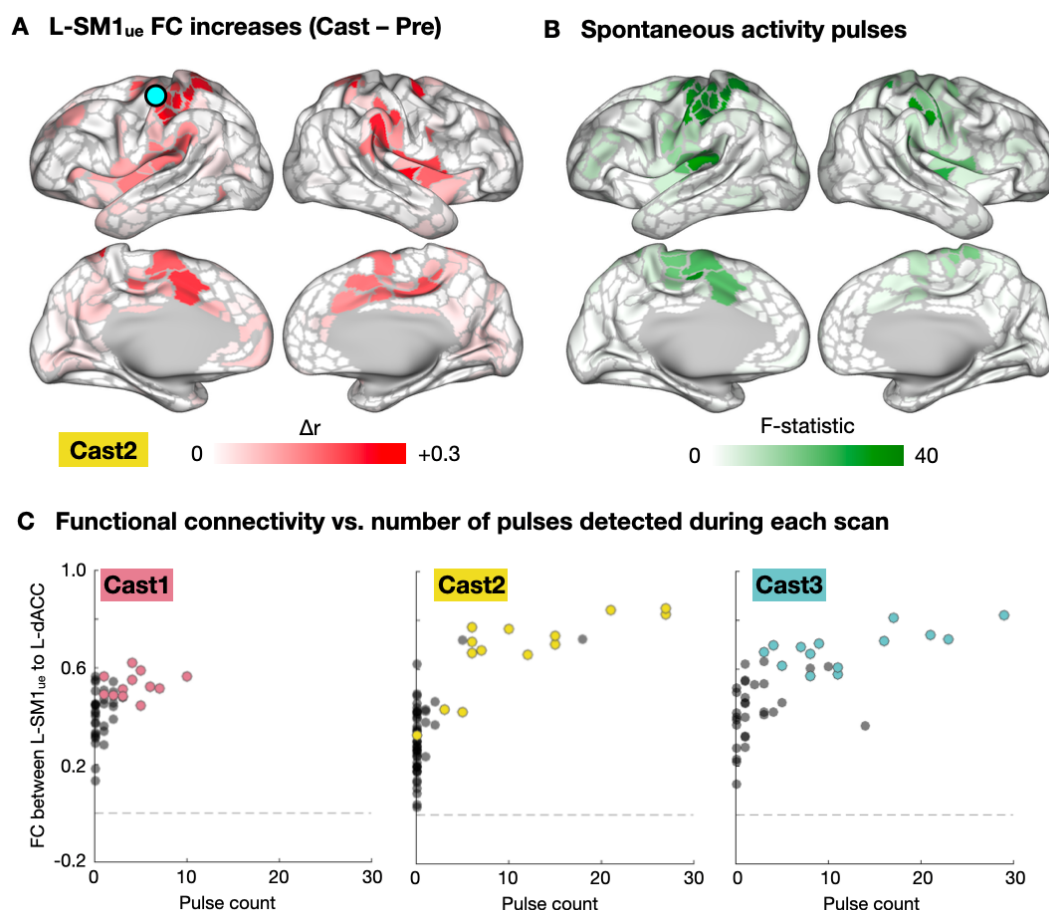
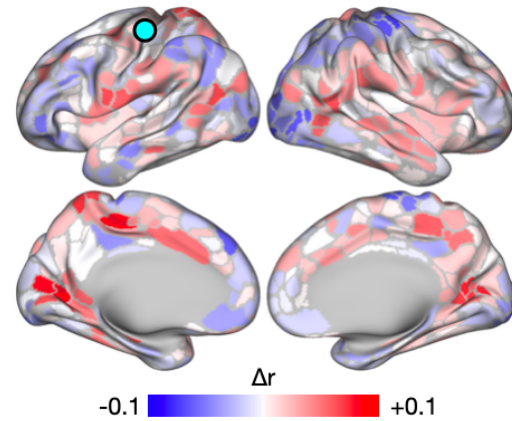
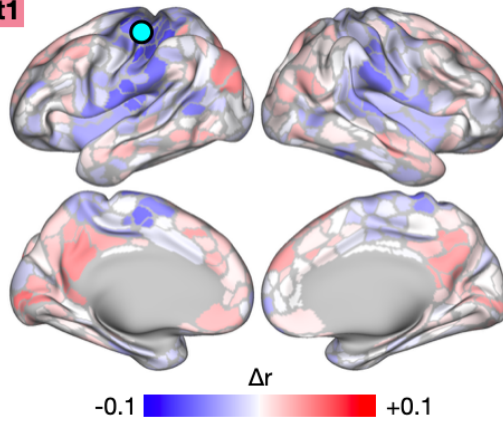


Fig. S5. Relationship of Spontaneous Activity Pulses to Functional Connectivity (FC) Changes. (A) Increases in FC with the disused somatomotor cortex (L-SM1_{ue}) during casting, repeated from Figure 2B for reference. (B) Analysis of variance (ANOVA) showing regions with spontaneous activity pulses. ANOVA F-statistic was correlated with FC change in each parcel (Cast1: $r = 0.16$, $P < 0.001$; Cast2: $r = 0.29$, $P < 0.001$; Cast3: $r = 0.06$, $P = 0.12$). (C) Relationship of FC between L-SM1_{ue} and the dorsal anterior cingulate cortex (dACC; cingulo-opercular network (CON)) vs. the number of pulses detected. Each dot represents one 30-minute scan. Colored dots represent scans during the cast period. For all participants, FC between L-SM1_{ue} and dACC was significantly correlated with the number of pulses detected (Cast1: $r = 0.74$, $P < 0.001$; Cast2: $r = 0.57$, $P < 0.001$; Cast3: $r = 0.73$, $P < 0.001$).

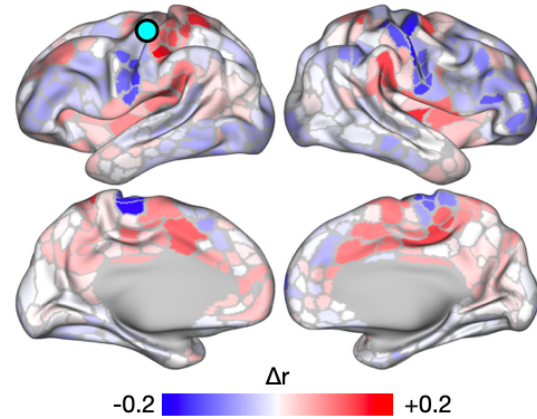
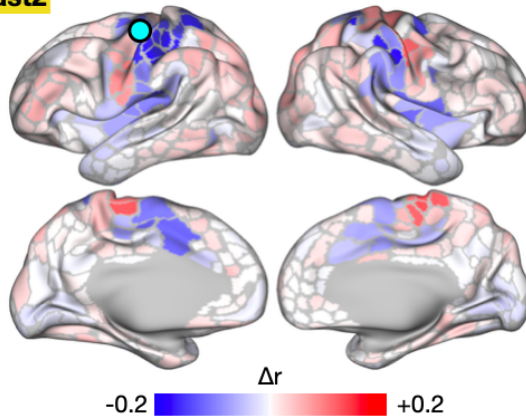
A Effect of pulse censoring (Cens - Cast)

B Residual effect (Cens - Pre)

Cast1



Cast2



Cast3

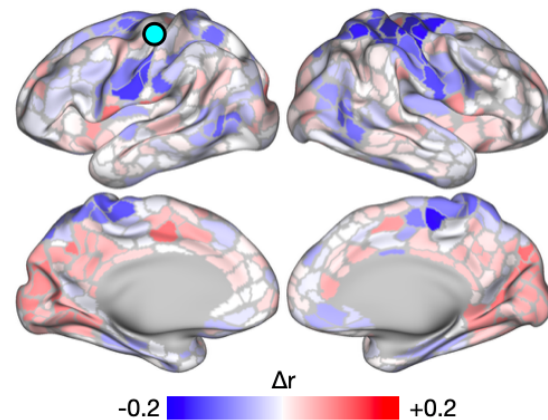
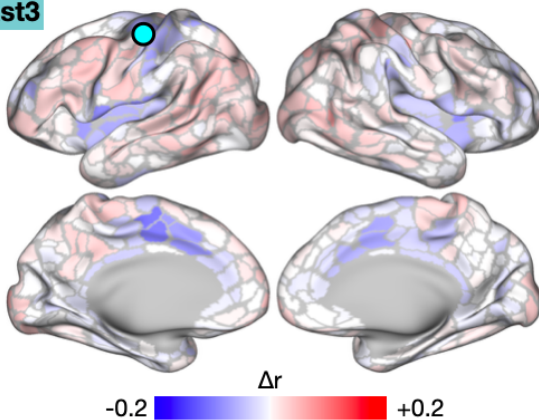
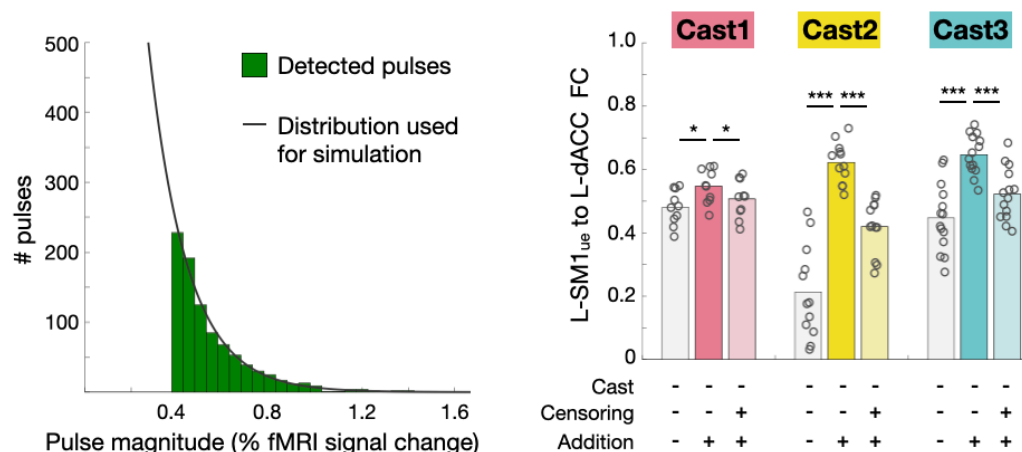


Fig. S6. Functional Connectivity (FC) Changes Explained by Spontaneous Activity Pulses. (A) Subtraction map showing changes in L-SM1_{ue} FC due to pulse censoring. The spatial pattern of FC changes due to pulse censoring was negatively correlated with FC changes during casting (Cast1: $r = -0.35$, $P < 0.001$; Cast2: $r = -0.90$, $P < 0.001$; Cast3: $r = -0.33$, $P < 0.001$). (B) Subtraction map showing residual FC changes during casting after pulse censoring. The spatial pattern of residual FC changes was negatively correlated with the effect of pulse censoring (Cast1: spatial correlation, $r = -0.23$, $P < 0.001$; Cast2: $r = -0.76$, $P < 0.001$; Cast3: $r = -0.18$; $P < 0.001$).

A Exponential distribution



B Triangular distribution

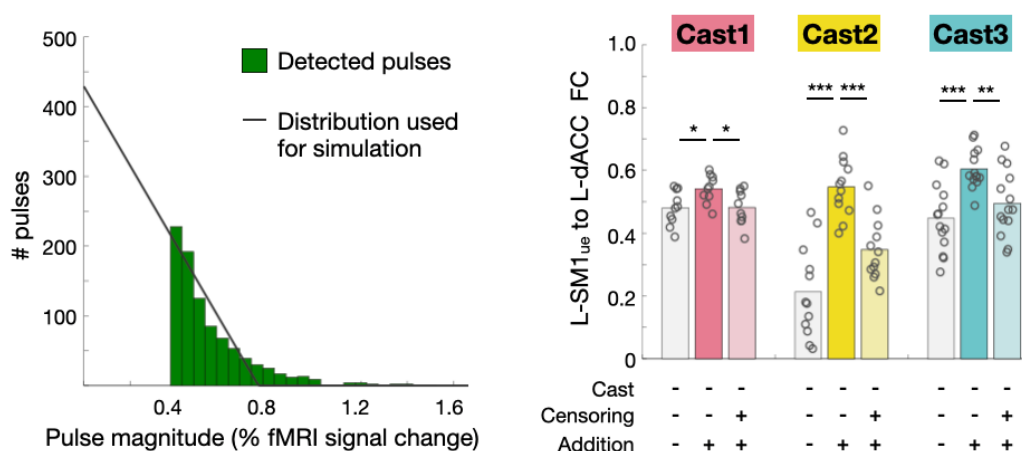
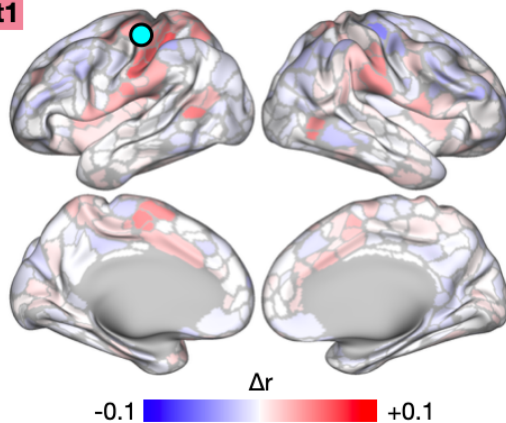


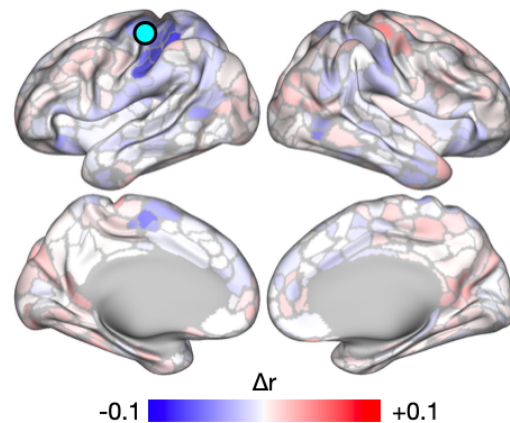
Fig. S7. Alternative Distributions for Pulse Magnitudes. (A) Exponential distribution. *Left:* Histogram of pulse magnitudes (peak fMRI signal), pooled across all participants. An exponential distribution (black line) was fit to the data using a least-squares approach. *Right:* Adding simulated pulses, with magnitudes drawn from the exponential distribution, increased FC between L-SM1_{ue} and L-dACC. Censoring simulated pulses partially reduced FC increases. *P<0.05, ***P<0.001. (B) Triangular distribution. *Left:* Histogram of pulse magnitudes (peak fMRI signal), pooled across all participants. A linear distribution (black line) was fit to the data using a least-squares approach. *Right:* Adding simulated pulses, with magnitudes drawn from the linear distribution, increased FC between L-SM1_{ue} and L-dACC. Censoring simulated pulses partially reduced FC increases. *P<0.05, **P<0.01, ***P<0.001.

A Effect of simulation (Sim - Pre)

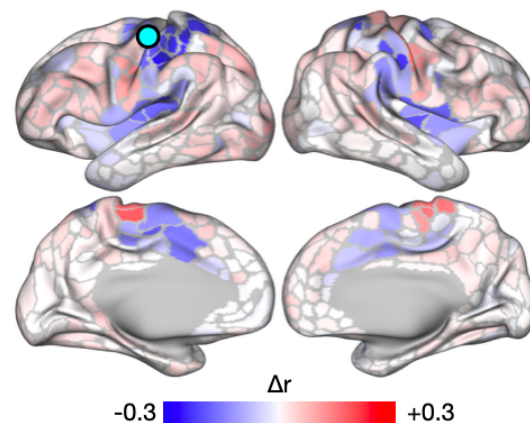
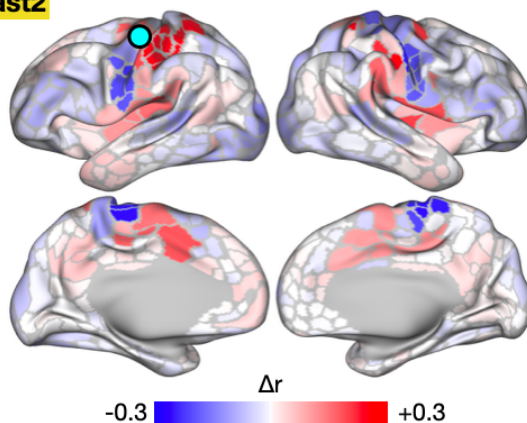
Cast1



B Effect of censoring (Cens - Sim)



Cast2



Cast3

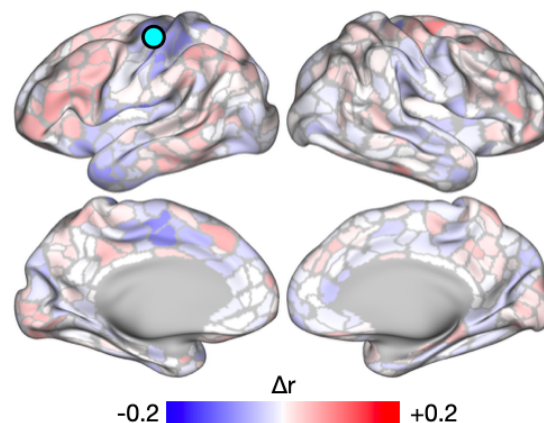
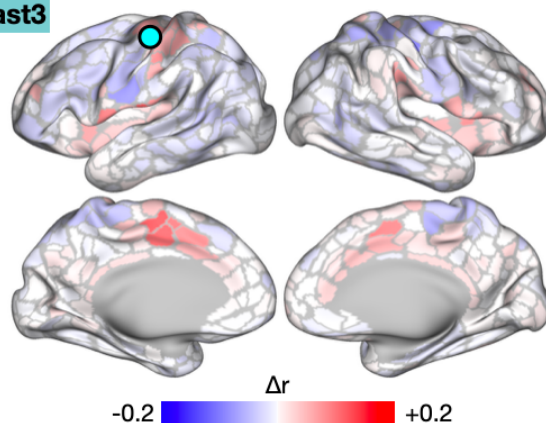
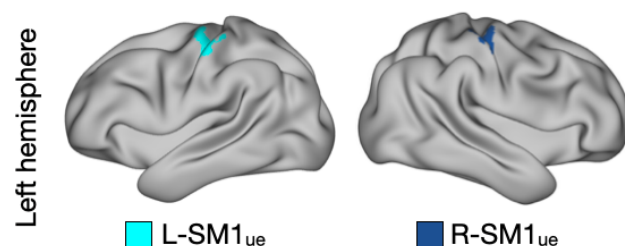
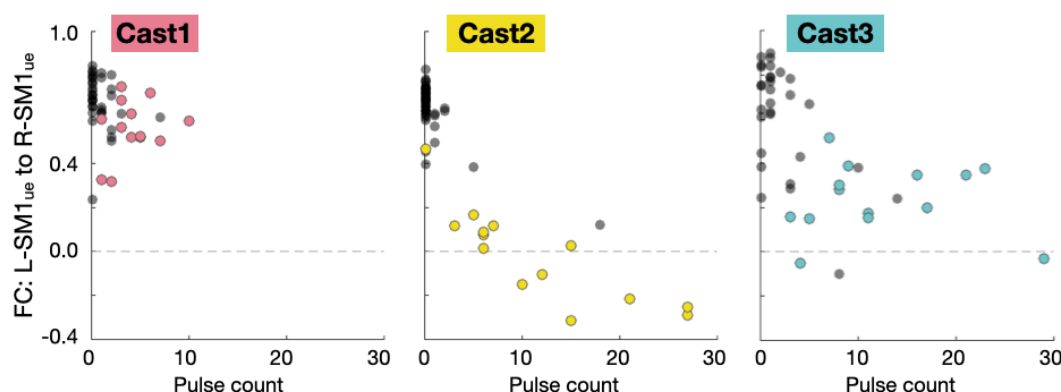


Fig. S8. Functional Connectivity (FC) Changes Caused by Simulated Spontaneous Activity Pulses (All Participants). (A) Subtraction map showing changes in L-SM1_{ue} FC due to addition of simulated pulses. FC changes due to pulse addition closely matched FC changes during casting (Cast1: spatial correlation, $r = 0.44$, $P < 0.001$; Cast2: $r = 0.95$, $P < 0.001$; Cast3: $r = 0.64$, $P < 0.001$). (B) Subtraction map showing effect of censoring simulated pulses. Effects of censoring closely complemented the effect of pulse addition (Cast1: $r = -0.71$, $P < 0.001$; Cast2: $r = -0.96$, $P < 0.001$; Cast3: $r = -0.69$, $P < 0.001$).

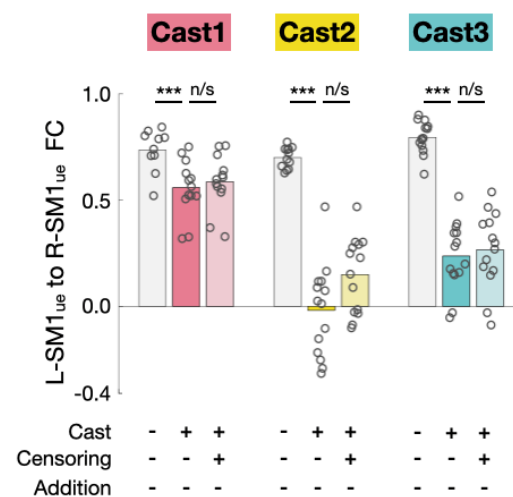
A Left and right motor regions of interest



B Functional connectivity vs. number of pulses detected during each scan



C Effect of pulse censoring



D Effect of pulse addition

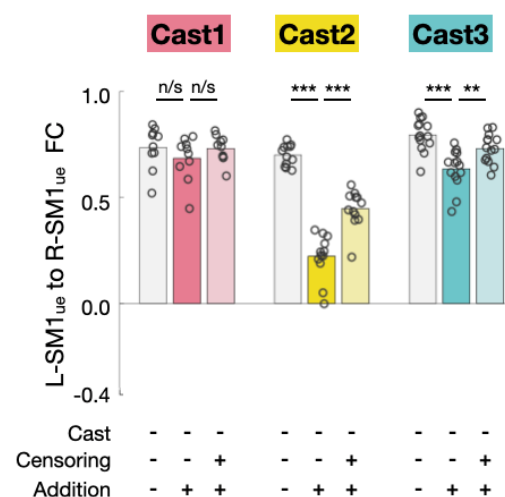


Fig. S9. Functional Connectivity (FC) Decreases Were Not Explained by Spontaneous Activity Pulses. (A) Example regions of interest (ROIs) in the left and right primary somatomotor cortex (L-SM1_{ue} and R-SM1_{ue}). (B) Relationship of FC between L-SM1_{ue} and R-SM1_{ue} vs. the number of pulses detected. Each dot represents one 30-minute scan. Colored dots represent scans during the cast period. For all participants, FC between L-SM1_{ue} and R-SM1_{ue} was significantly correlated with the number of pulses detected (Cast1: $r=0.74$, $P<0.001$; Cast2: $r=0.57$, $P<0.001$; Cast3: $r=0.73$, $P<0.001$). (C) Censoring pulses did not reduce the difference between Pre and Cast scans. *** $P < 0.001$. (D) Adding simulated pulses decreased FC between L-SM1_{ue} and R-SM1_{ue} in two participants (Cast2 and Cast3), but these decreases were much smaller than those observed during casting. *** $P < 0.001$. ** $P < 0.01$.

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