Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Tracking plasticity of individual human brains

Dillan J Newbold[1] and Nico UF Dosenbach[1,2,3,4,5]

Understanding how behavior affects human brain organization was the original motivation behind Precision Functional Mapping (PFM), a deep phenotyping approach to human neuroimaging. Here we review the original PFM studies, as well as research investigating the impact of sensory and/or motor deprivation, or disuse, on brain function. Next, we discuss precision functional mapping of brain plasticity, focusing on experiments that tracked casting of the dominant upper extremity with daily resting-state functional MRI scans. Mechanisms that shape brain circuits during early development may persist into adulthood, helping to maintain the organization of disused circuits.

Addresses
[1] Department of Neurology – Washington University School of Medicine, St. Louis, MO, 63110, USA
[2] Department of Radiology – Washington University School of Medicine, St. Louis, MO, 63110, USA
[3] Department of Pediatrics – Washington University School of Medicine, St. Louis, MO, 63110, USA
[4] Program in Occupational Therapy – Washington University School of Medicine, St. Louis, MO, 63110, USA
[5] Department of Biomedical Engineering – Washington University in St. Louis, St. Louis, MO, 63130, USA

Corresponding authors:
Newbold, Dillan J (newbold@wustl.edu), Dosenbach, Nico UF (dosenbachn@wustl.edu)

Current Opinion in Behavioral Sciences 2021, **40**:161–168

This review comes from a themed issue on **Deep imaging – personalized neuroscience**

Edited by **Caterina Gratton** and **Rodrigo Martin Braga**

https://doi.org/10.1016/j.cobeha.2021.04.018

Introduction

Plasticity is the process that shapes brain circuits during development and continually refines them throughout life. A crucial part of typical developmental plasticity is the active use of brain circuits [1,2]. Regular use may also be required to maintain circuits throughout life. Disuse greatly reduces the feedback by which motor circuits maintain an accurate representation of the body or the outside world. Thus, behavioral disuse can cause systematic reorganization of affected circuits and lead to deterioration of function [3•,4].

What mechanisms does the brain have to protect circuits during periods of relative disuse? Internally generated spontaneous activity might play a role in circuit stability and plasticity. Spontaneous activity helps to shape circuits early in development, before they have had any contact with the outside world [1,2,5,6]. Similar mechanisms may still be available to the adult brain to maintain and reorganize large-scale brain circuits during disuse. Here, we review neuroscientific research into disuse-driven plasticity, including early work in animal models and later advances from human studies. We also describe our recent upper extremity casting study, which drove functional network plasticity in three highly sampled humans, suggesting novel mechanisms by which spontaneous activity shapes and maintains human brain circuits [7••,8••].

Disuse-driven neural plasticity

A great deal of progress in neuroscience has come from experiments that blocked the normal interactions between brain circuits and the outside world. Suturing one eye shut showed that ocular dominance columns in the primary visual cortex are shaped by use-driven plasticity, as afferents from the two eyes compete with one another for representational territory [9,10]. Severing the median nerve of an upper limb [11•], amputating a digit [12], and casting one upper extremity [3•] revealed similar use-driven plasticity mechanisms in the primary somatosensory and motor cortex.

Map plasticity proceeds through two phases [13]. Immediately after deafferentation, some neurons in the deafferented cortical area begin to respond to previously silent afferent inputs, a phenomenon termed 'unmasking'. Then, over the course of several weeks, new sensory representations fill the deafferented cortex and are gradually refined into a smooth somatotopic map. Later work revealed that unmasking is mediated, at least in part, by focal disinhibition of disused cortex, evident as local reductions in gamma amino butyric acid (GABA) [14] and GABA receptors [15]. The gradual remapping process that occurs after unmasking appears to be driven by activity-dependent plasticity, because this gradual remapping, but not the initial unmasking, is blocked by chronic administration of an NMDA-receptor antagonist [16].

Altered physiology of inhibitory interneurons is not only important for acute unmasking during disuse but may be crucial for permitting plasticity more broadly. Plasticity of a given brain region is greatest during critical periods [17]. The maturation of parvalbumin-positive interneurons is a

key factor permitting critical period plasticity [18]. Mice lacking one isoform of glutamic acid decarboxylase (GAD65), an enzyme responsible for the synthesis of GABA, never enter a critical period [19]. This deficit can be reversed by diazepam, a GABA agonist [20]. Additionally, transplantation of immature inhibitory interneurons permits critical period-like plasticity in the adult cortex [21,22]. Disinhibition following disuse may therefore represent a form of developmental regression that 'reopens' a critical period-like physiological state and enhances adult plasticity [23,24].

Plasticity and spontaneous neural activity

Retinotopic organization of V1 is present even before visual experience [5]. Development of retinotopic maps before visual experience depends on a combination of genetically encoded axon guidance cues and spontaneous neural activity [6]. Once a rough retinotopic map is established in V1 by molecular guidance cues, retinotopy is further refined by waves of spontaneous activity that originate in the retina. Retinal waves trigger similar waves of activity in higher visual structures, including the superior colliculus and primary and secondary visual cortex [25••]. Co-activation of neighboring retinal ganglion cells during spontaneous retinal waves refines retinotopic maps in downstream structures [26–29].

A similar form of spontaneous activity helps shape somatomotor maps [1,2]. Embryological movements are triggered by waves of spontaneous activity that propagate between motor neurons in the spinal cord [30,31]. Patterned somatosensory feedback resulting from spontaneous movements is thought to promote self-organization of pattern-generating circuits in the spinal cord [32].

Early in development, prenatal brain activity shows a discontinuous pattern, in which brief waves of spontaneous activity are separated by long periods of silence [33]. The brief waves depolarize nearly all of the neurons in a given brain region and the long period of silence result from neuronal refractory periods [31]. Later in development, at the onset of critical periods, newly matured GABAergic interneurons begin to dampen spontaneous waves of activity [34]. As spontaneous waves of activity become smaller and the interleaved refractory periods become shorter [33], the dynamics of spontaneous brain activity shift from a pattern of brief, transient waves to an ongoing, Gaussian process of many superimposed fluctuations. Spontaneous activity in the adult brain typically lacks the transient dynamics seen early in development [35].

Human plasticity studies

Brain regions do not function in isolation but instead cooperate with other regions to perform specific cognitive operations. The concept of brain networks—sets of cooperating brain regions—has existed for several decades [36]. Non-invasive, whole-brain imaging has made it possible to study brain networks directly in the human brain.

The vast majority of the brain's energy is expended on spontaneous activity [37]. The largest fluctuations in spontaneous activity occur at an infra-slow time scale (<0.1 Hz), which means that they can be monitored using fMRI [38]. Correlations in these fluctuations across brain regions are known as 'functional connectivity.' Functional connectivity (FC) has been used to divide the brain into a number of canonical functional networks. Some key brain networks include the visual, auditory and somatomotor networks [39,40]; the ventral and dorsal attention networks [41,42]; the default mode network with roles in internally directed cognition and episodic memory [43,44]; the salience network thought to assess the homeostatic relevance of external stimuli [45]; the frontoparietal control network supporting error-processing and moment-to-moment adjustments in behavior [46–48]; and the cingulo-opercular control network (CON), which maintains executive control during goal-directed behavior [46,47,49].

Several prior studies have induced changes in human behavior or experience hoping to measure plasticity with resting state fMRI (rs-fMRI). Lewis *et al.* used a visual discrimination task to train participants to focus their attention on one visual quadrant [50•]. They reported many different changes in FC throughout the brain, but the most compelling of these effects was a decrease in FC between the dorsal attention network and the trained quadrant of V1. They also found increased FC between the untrained regions of V1 and the default mode network. At least two separate studies have scanned participants before and after training on a visuomotor adaptation task. Albert *et al.* reported increased FC in a fronto-parietal network and in multiple regions of the cerebellum following motor adaptation training [51]. Shannon *et al.* found reduced FC between a ventrolateral premotor region (Brodmann Area 44) and the primary visual cortex [52]. These and similar studies [53–55] all reported small changes in FC ($\Delta r \sim 0.1$) following training. Conversely, repeated sampling studies have shown FC to be very stable across time, in the absence of specific interventions [56•,57].

FC can be altered more drastically by brain lesions. For example, brain plasticity can allow for typical cognitive abilies, despite losing ~25% of cortical tissue to bilateral perinatal strokes [58]. Patients that have suffered strokes of the corticospinal tract (CST) can show markedly reduced FC ($\Delta r \sim 0.5$) between the left and right motor cortex [59]. For patients with mild CST damage, higher FC (more similar to control participants) predicted greater strength and fine motor function [59]. A related

finding is reduced FC in patients missing one hand, either due to congenital malformation [60] or amputation [61].

Measurement noise, differences in behavioral state, and inter-individual variability induce variance in FC [57]. Classical group averaging to deal with noise is problematic because individuals differ in their functional neuroanatomy [62]. A more recent approach to dealing with measurement variability is to collect extensive rs-fMRI data (a minimum of 30 min) in each participant and carry out analyses separately in each individual, an approach we have termed Precision Functional Mapping (PFM, Figure 1). Russell Poldrack's MyConnectome Project [63•], in which he scanned himself twice per week for an entire year, served as an inspiration for our Midnight Scan Club (MSC) study. For the MSC, we collected 10 highly sampled individual-specific rs-fMRI datasets [64•]. The MSC data have been used to generate individual-specific maps of cortex [64], cerebellum [65], thalamus [66], amygdala [67], hippocampus [68] and striatum [69]. Individual differences in functional connectivity architecture also exist in the mouse brain [70]. In addition to identifying individual differences, PFM enables finer-scale network parcellations [71,72] and tracking of FC changes across time [7••,63,73,74].

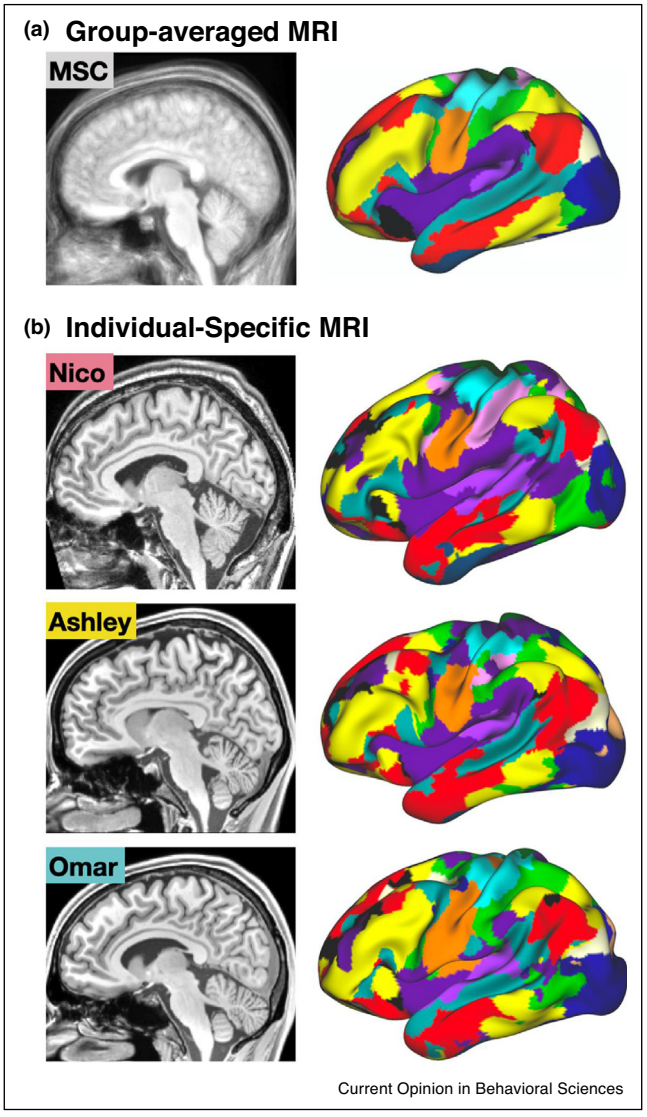
Precise tracking of brain plasticity during limb constraint

We recently demonstrated that PFM can be used to track the time course of disuse-driven plasticity in the human brain [7••]. Three adult participants (Nico, Ashley and Omar) were scanned at the same time of day for 42–64 consecutive days (30 min of rs-fMRI/day) before, during and after two weeks of dominant upper extremity casting (Figure 2).

Casting had profound effects on behavior and motor function. Constant behavioral monitoring using accelerometers on both wrists showed large reductions in use of the casted extremity (−50%) and slight increases in use of the un-casted extremity (+20%). Motor assessments completed immediately after cast removal showed large reductions in grip strength (−40 lb) and fine motor skill (−20% performance on Purdue Pegboard) of the casted extremity. We did not observe consistent changes in strength or fine motor skill of the un-casted extremity.

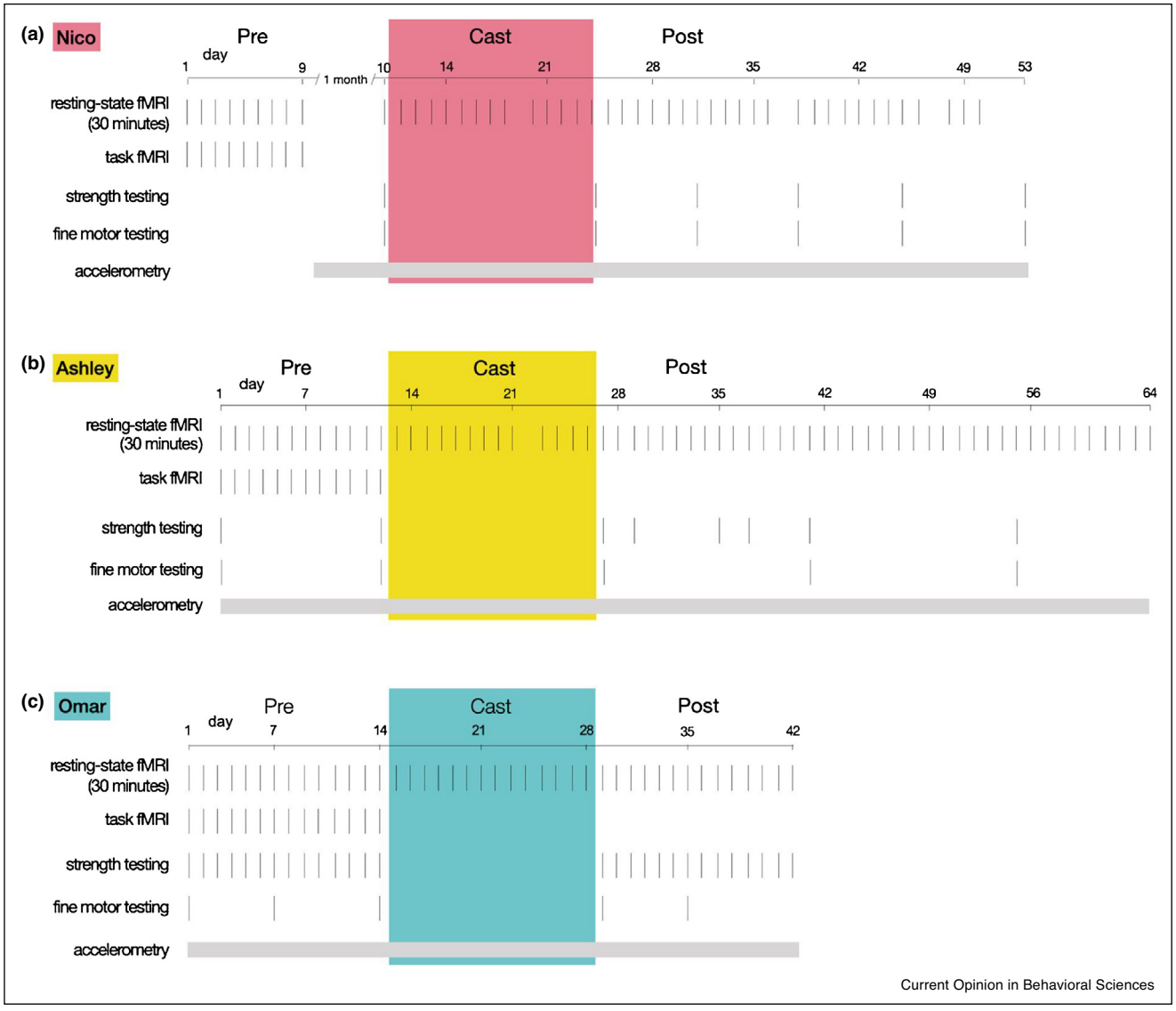
Daily rs-fMRI scans before, during and after casting in three volunteers (Nico, Ashley, Omar) revealed multiple changes in spontaneous activity of disused brain circuits. The most striking observation was of large, spontaneous pulses of activity that occurred in the disused motor circuits during casting (Figure 3). No pulses were observed before casting, many pulses were detected during the cast period, and a small number of pulses occurred after cast removal. Pulses had a waveform resembling a canonical hemodynamic response function, consistent with a brief burst of neural activity. In addition to the disused motor cortex, pulses also occurred in the dorsal anterior cingulate cortex/supplementary motor area (dACC/SMA), anterior insula, secondary somatosensory

Figure?1



Precision functional mapping.
(a) Group-averaged images based on a combination of all 10? participants from the Midnight Scan Club (MSC) experiment [64•]. *Left:* Average T1-weighted structural image demonstrates the loss of focal information due to group averaging. *Right:* An average functional network map captures the general functional organization of the brain but lacks the detailed features present in individual-specific maps. Each color represents a different functional network. **(b)** Individual-specific images of the three participants in the Cast-Induced Plasticity Experiment [7••]. *Left:* T1-weighted structural images from each participant demonstrate individual-specific features of structural anatomy. *Right:* Individual-specific functional network maps reveal unique features of functional anatomy not apparent in the group-averaged map.

Figure?2



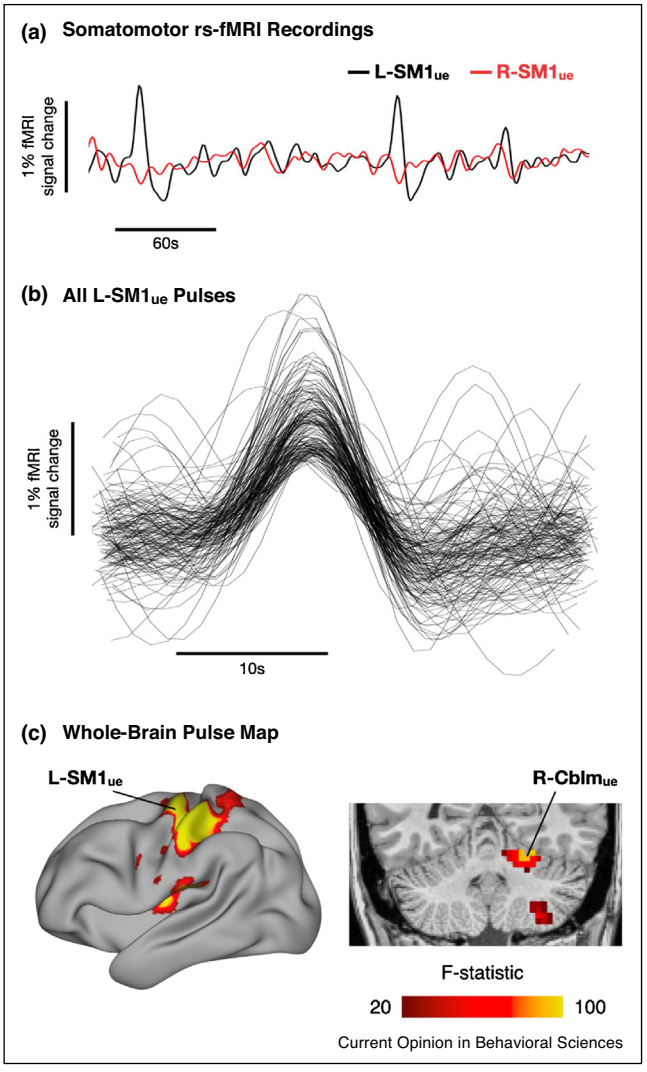
Experimental design.
Data acquisition included resting-state functional MRI (rs-fMRI), task-based functional MRI (fMRI), strength testing, fine motor testing, and constant behavioral monitoring using wearable accelerometers. Full experimental designs are shown for all three participants – Nico **(a)**, Ashley **(b)**, and Omar **(c)**.

cortex (SII), pre- and post-central sulci, angular gyri, putamen, thalamus and cerebellum. Collectively, these regions comprise the somatomotor circuit that normally controls the casted extremity, as well as the cingulo-opercular network (CON).

All participants showed highly consistent, rapid, and anatomically specific changes in FC (Figure 4). The most prominent change was a loss of typical FC between the disused motor cortex (L-$SM1_{ue}$) and the homotopic region of the opposite hemisphere (R-$SM1_{ue}$). All participants showed large effect sizes (Nico: $\Delta r = -0.23$, Ashley: $\Delta r = -0.86$, Omar: $\Delta r = -0.61$). Loss of FC between L-$SM1_{ue}$ and R-$SM1_{ue}$ occurred rapidly during casting, with significant decreases detectable in all participants within 48 hours of casting. Recovery was rapid in two participants, while one participant (Omar) continued to show diminished FC for two weeks after cast removal. L-$SM1_{ue}$ disconnected not only from R-$SM1_{ue}$, but also from the remainder of the somatomotor network [7••].

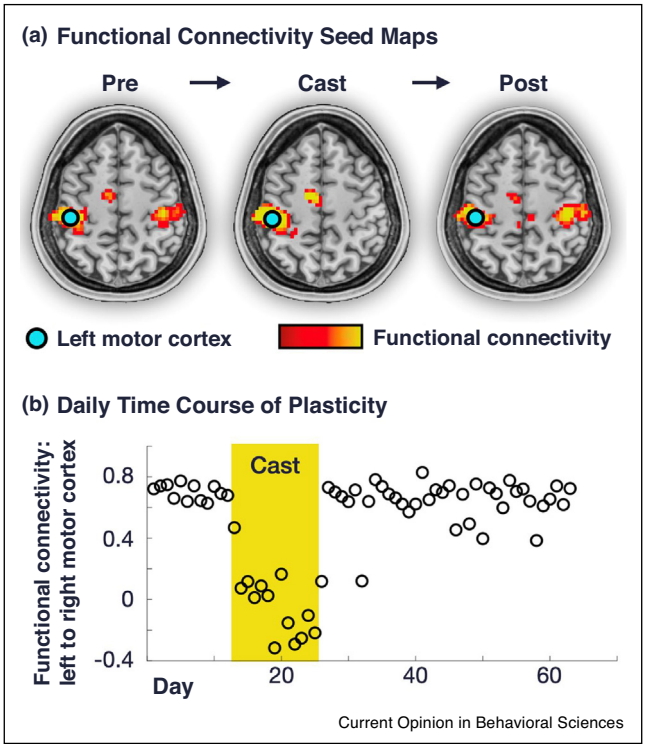
L-$SM1_{ue}$ also showed increased FC with the dACC/SMA, anterior insula, SII, bilateral pre- and post-central sulci and angular gyri, as well as regions of the putamen,

Figure?3



Spontaneous activity pulses in disused circuits.
(a) Resting-state functional MRI (rs-fMRI) signals recorded from left and right primary somatomotor cortex (L-SM1$_{ue}$ and R-SM1$_{ue}$) during the casting period. Several large pulses of spontaneous activity occur in the disused L-SM1$_{ue}$. **(b)** Recordings of 144?pulses detected in one participant (Ashley), superimposed on one another. Pulses had a consistent shape resembling a canonical hemodynamic response function, consistent with a brief burst of neural activity. **(c)** Whole-brain analysis of variance (ANOVA) showing synchronized pulses in the left somatomotor cortex, left insula, and right cerebellum. Pulses also occurred in the left dorsal anterior cingulate cortex (dACC, not shown).

Figure?4



Functional disconnection of disused circuits.
(a) Seed maps showing functional connectivity between the left primary motor cortex (blue dot) and the rest of the brain before (Pre), during (Cast) and after casting (Post). Results are shown for one example participant (Ashley). Before casting, the left motor cortex showed strong homotopic functional connectivity (FC) with the contralateral motor cortex, as well as ipsilateral FC with the supplementary motor cortex. Homotopic FC was lost during casting and then regained after cast removal. **(b)** Daily time course of homotopic motor FC. FC was highly stable before casting and decreased rapidly during casting. FC continued to weaken throughout the cast period and then returned to baseline within 2?days after cast removal.

thalamus and cerebellum. FC increases were highly specific to the CON and did not involve any other functional networks. Increased FC between L-SM1$_{ue}$ and the CON appeared to result from the spontaneous activity pulses that occurred synchronously in both structures. Censoring pulses partially reversed cast-driven FC increases. Addition of simulated pulses recreated cast-driven FC increases. Applying these same censoring and additional analyses to cast-driven decreases in FC between homotopic somatomotor regions suggested that the plasticity pulses could not explain FC decreases during casting [8••].

Conclusions

Brain circuits require regular use to maintain their functional architecture

One hypothesis regarding the spatiotemporal organization of spontaneous activity is that resting-state FC results from prior coactivation of brain regions during behavior and experience [47,50•,52,75,76]. This is often called a 'Hebbian-like' account of FC, which suggests that brain regions that co-activate during behavior show stronger FC during subsequent rest. The massive reductions in FC ($\Delta r \sim 0.8$) due to casting-driven disuse represent some of

the strongest evidence found to date that co-use can affect FC. The casting experiment also provided additional insights into the timescales of disuse-driven FC changes. Blocking co-use of the left and right upper extremities causes near-complete loss of FC between the left and right motor cortex in a matter of one to two days.

Precision functional mapping enables reliable tracking of plasticity

The anatomically specific, large-magnitude changes in FC observed during casting can partly be attributed to the dramatic behavioral manipulation we imposed (two weeks of persistent limb constraint) and the large amount of data we collected on each participant (21–32 hours of rs-fMRI per participant). The reliability of FC measurement increases drastically with increasing duration of recordings [56•]. Typical studies acquire very little data (often <10 min) on each participant. Such short scans yield very noisy measurements of FC and would provide little statistical power to detect FC changes due to an experimental manipulation. The novel experimental design we used to examine FC changes during casting could easily be applied to study other plasticity manipulations, fluctuations in hormone levels [73], progression of psychiatric and neurological diseases, or responses to therapies. In a time when the more common approach of cross-sectionally correlating individual-differences with naturally occurring variance in behavioral trait measures is facing a replication crisis [77], PFM can provide an alternate path forward for relating rs-fMRI measures to behavioral and clinical variables.

Spontaneous activity pulses may help maintain disused circuits

The brain may have mechanisms that at least temporarily protect circuits during disuse. Adult brain circuits are typically maintained by regular use [1]. Spontaneous neural activity may help protect circuits from disuse-driven functional degradation.

Spontaneous waves of activity typically cease early in critical periods [31,33], when the brain begins to rely on external inputs to shape circuits. At critical-period onset, inhibition by parvalbumin-positive interneurons increases [18,34]. Increased inhibitory tone remains into adulthood and spontaneous activity in the adult brain typically does not include the transient waves of activity seen in pre-critical period development. However, following the onset of disuse, parvalbumin-expressing interneurons in disused circuits become less active, shifting the excitatory-inhibitory balance in these circuits towards a more development-like state [78]. Focal disinhibition during disuse may permit the reemergence of spontaneous waves of activity, even in the adult brain. If so, these waves of activity may help maintain the somatotopic organization that is shared across regions throughout the somatomotor system. Closer examination of spontaneous activity pulses may reveal new targets by which to promote maintenance and recovery of function in the setting of clinical disuse or brain injury.

Conflict of interest statement

NUFD is the co-founder of NOUS Imaging Inc.

Acknowledgements

This work was supported by N.I.H. grants NS110332 (D.J.N.),NS088590 (N.U.F.D.), MH96773 (N.U.F.D.), MH122066 (N.U.F.D.), MH124567 (N.U.F.D.), MH121276 (N.U.F.D.); Kiwanis Neuroscience Research Foundation (N.U.F.D.); the Jacobs Foundation grant 2016121703 (N.U.F.D.); the Child Neurology Foundation (N.U.F.D.); the McDonnell Center for Systems Neuroscience (N.U.F.D.); the Mallinckrodt Institute of Radiology grant 14-011 (N.U.F.D.); the Hope Center for Neurological Disorders (N.U.F.D.).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Buzsa'ki G: *The Brain from Inside Out Brain*. New York, NY: Oxford University Press; 2019. xvii, 441 pages.

2. Blumberg MS, Marques HG, Iida F: **Twitching in sensorimotor development from sleeping rats to robots**. *Curr Biol* 2013, **23**: R532-R537.

3. • Milliken GW, Plautz EJ, Nudo RJ: **Distal forelimb representations in primary motor cortex are redistributed after forelimb restriction: a longitudinal study in adult squirrel monkeys**. *J Neurophysiol* 2013, **109**:1268-1282.
Motor disuse experiment in non-human primates. Casting one upper extremity several weeks caused reorganization of somatotopic maps in the primary motor cortex, similar to the somatosensory reorganization shown by previous sensory disuse experiments. After casting, distal representations of the casted upper extremity lost territory in the primary motor cortex. This effect reversed after cast removal.

4. Clark BC *et al.*: **Neuromuscular plasticity during and following 3 wk of human forearm cast immobilization**. *J Appl Physiol (1985)* 2008, **105**:868-878.

5. Wiesel TN, Hubel DH: **Ordered arrangement of orientation columns in monkeys lacking visual experience**. *J Comp Neurol* 1974, **158**:307-318.

6. Espinosa JS, Stryker MP: **Development and plasticity of the primary visual cortex**. *Neuron* 2012, **75**:230-249.

7. •• Newbold DJ *et al.*: **Plasticity and spontaneous activity pulses in disused human brain circuits**. *Neuron* 2020, **107**:580-589 e6.
Original article describing the casting-induced plasticity study, which involved casting the dominant upper extremity of three volunteers and tracking resting state functional connectivity (RSFC) changes with daily MRIs. Focused on the functional disconnection between disused primary somatomotor cortex and the rest of the somatomotor system. Initial demonstration of spontaneous activity pulses in disused somatomotor circuits.

8. •• Newbold DJ *et al.*: **Cingulo-opercular control network and disused motor circuits joined in standby mode**. *Proc Natl Acad Sci U S A* 2021, **118**.
Examination of whole-brain effects of cast-induced plasticity. Revealed increased functional connectivity between disused motor circuitry and motor control regions belonging to the cingulo-opercular network (CON), thought to be important for executive control. Suggests that spontaneous activity pulses may help maintain functional connectivity of disused motor circuits.

9. Wiesel TN, Hubel DH: **Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens**. *J Neurophysiol* 1965, **28**:1029-1040.

10. Wiesel TN, Hubel DH: **Single-cell responses in striate cortex of kittens deprived of vision in one eye**. *J Neurophysiol* 1963, **26**:1003-1017.

11. • Merzenich MM *et al.*: **Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation**. *Neuroscience* 1983, **8**:33-55.
Original demonstration of map plasticity in the primary somatosensory cortex following sensory disuse. Ligation of the median nerve of one upper extremity causes deafferented sensory representations to lose territory in the primary somatosensory cortex.

12. Merzenich MM *et al.*: **Somatosensory cortical map changes following digit amputation in adult monkeys**. *J Comp Neurol* 1984, **224**:591-605.

13. Merzenich MM *et al.*: **Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys**. *Neuroscience* 1983, **10**:639-665.

14. Garraghty PE, LaChica EA, Kaas JH: **Injury-induced reorganization of somatosensory cortex is accompanied by reductions in GABA staining**. *Somatosens Mot Res* 1991, **8**:347-354.

15. Wellman CL *et al.*: **Acute reductions in GABAA receptor binding in layer IV of adult primate somatosensory cortex after peripheral nerve injury**. *Brain Res* 2002, **954**:68-72.

16. Garraghty PE, Muja N: **NMDA receptors and plasticity in adult primate somatosensory cortex**. *J Comp Neurol* 1996, **367**:319-326.

17. Hubel DH, Wiesel TN: **The period of susceptibility to the physiological effects of unilateral eye closure in kittens**. *J Physiol* 1970, **206**:419-436.

18. Hensch TK: **Critical period regulation**. *Annu Rev Neurosci* 2004, **27**:549-579.

19. Hensch TK, Local GABA *et al.*: **circuit control of experience-dependent plasticity in developing visual cortex**. *Science* 1998, **282**:1504-1508.

20. Fagiolini M, Hensch TK: **Inhibitory threshold for critical-period activation in primary visual cortex**. *Nature* 2000, **404**:183-186.

21. Southwell DG *et al.*: **Cortical plasticity induced by inhibitory neuron transplantation**. *Science* 2010, **327**:1145-1148.

22. Tang Y *et al.*: **Cortical plasticity induced by transplantation of embryonic somatostatin or parvalbumin interneurons**. *Proc Natl Acad Sci U S A* 2014, **111**:18339-18344.

23. Harauzov A *et al.*: **Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity**. *J Neurosci* 2010, **30**:361-371.

24. Letzkus JJ, Wolff SB, Luthi A: **Disinhibition, a circuit mechanism for associative learning and memory**. *Neuron* 2015, **88**:264-276.

25. •• Ackman JB, Burbridge TJ, Crair MC: **Retinal waves coordinate patterned activity throughout the developing visual system**. *Nature* 2012, **490**:219-225.
Detailed examination of retinal waves *in vivo* in the developing mouse visual system. Voltage-sensative dyes and genetically encoded calcium indicators allow first-ever demonstration that retinal waves propagate through multiple cortical and subcortical visual regions.

26. Meister M *et al.*: **Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina**. *Science* 1991, **252**:939-943.

27. Wong RO: **Retinal waves and visual system development**. *Annu Rev Neurosci* 1999, **22**:29-47.

28. Butts DA, Kanold PO, Shatz CJ: **A burst-based "Hebbian" learning rule at retinogeniculate synapses links retinal waves to activity-dependent refinement**. *PLoS Biol* 2007, **5**:e61.

29. Kim J *et al.*: **Spontaneous retinal waves can generate long-range horizontal connectivity in visual cortex**. *J Neurosci* 2020, **40**:6584-6599.

30. Provine RR: **Ontogeny of bioelectric activity in the spinal cord of the chick embryo and its behavioral implications**. *Brain Res* 1972, **41**:365-378.

31. Blankenship AG, Feller MB: **Mechanisms underlying spontaneous patterned activity in developing neural circuits**. *Nat Rev Neurosci* 2010, **11**:18-29.

32. Petersson P *et al.*: **Spontaneous muscle twitches during sleep guide spinal self-organization**. *Nature* 2003, **424**:72-75.

33. Tolonen M *et al.*: **Development of the spontaneous activity transients and ongoing cortical activity in human preterm babies**. *Neuroscience* 2007, **145**:997-1006.

34. Toyoizumi T *et al.*: **A theory of the transition to critical period plasticity: inhibition selectively suppresses spontaneous activity**. *Neuron* 2013, **80**:51-63.

35. Laumann TO *et al.*: **On the stability of BOLD fMRI correlations**. *Cereb Cortex* 2017, **27**:4719-4732.

36. Posner MI, Petersen SE: **The attention system of the human brain**. *Annu Rev Neurosci* 1990, **13**:25-42.

37. Raichle ME: **Neuroscience. The brain's dark energy**. *Science* 2006, **314**:1249-1250.

38. Biswal B *et al.*: **Functional connectivity in the motor cortex of resting human brain using echo-planar MRI**. *Magn Reson Med* 1995, **34**:537-541.

39. Cordes D *et al.*: **Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data**. *AJNR Am J Neuroradiol* 2001, **22**:1326-1333.

40. Lowe MJ, Mock BJ, Sorenson JA: **Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations**. *Neuroimage* 1998, **7**:119-132.

41. Shulman GL *et al.*: **Multiple neural correlates of detection in the human brain**. *Proc Natl Acad Sci U S A* 2001, **98**:313-318.

42. Fox MD *et al.*: **Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems**. *Proc Natl Acad Sci U S A* 2006, **103**:10046-10051.

43. Raichle ME *et al.*: **A default mode of brain function**. *Proc Natl Acad Sci U S A* 2001, **98**:676-682.

44. Greicius MD *et al.*: **Functional connectivity in the resting brain: a network analysis of the default mode hypothesis**. *Proc Natl Acad Sci U S A* 2003, **100**:253-258.

45. Seeley WW *et al.*: **Dissociable intrinsic connectivity networks for salience processing and executive control**. *J Neurosci* 2007, **27**:2349-2356.

46. Dosenbach NU *et al.*: **Distinct brain networks for adaptive and stable task control in humans**. *Proc Natl Acad Sci U S A* 2007, **104**:11073-11078.

47. Dosenbach NU *et al.*: **A dual-networks architecture of top-down control**. *Trends Cogn Sci* 2008, **12**:99-105.

48. Marek S, Dosenbach NUF: **Control networks of the frontal lobes**. *Handb Clin Neurol* 2019, **163**:333-347.

49. Dosenbach NU *et al.*: **A core system for the implementation of task sets**. *Neuron* 2006, **50**:799-812.

50. • Lewis CM *et al.*: **Learning sculpts the spontaneous activity of the resting human brain**. *Proc Natl Acad Sci U S A* 2009, **106**:17558-17563.
Group-averaged resting state functional connectivity (RSFC) study that provided evidence of adult functional network plasticity in response to a training paradigm. Participants were trained on a shape-identification task constrained to one visual quadrant, which altered RSFC between trained visual cortex and frontal-parietal areas involved in the control of spatial attention.

51. Albert NB, Robertson EM, Miall RC: **The resting human brain and motor learning**. *Curr Biol* 2009, **19**:1023-1027.

52. Shannon BJ *et al.*: **Brain aerobic glycolysis and motor adaptation learning**. *Proc Natl Acad Sci U S A* 2016, **113**:E3782-91.

53. Sami S, Robertson EM, Miall RC: **The time course of task-specific memory consolidation effects in resting state networks**. *J Neurosci* 2014, **34**:3982-3992.

54. Vahdat S *et al.*: **Functionally specific changes in resting-state sensorimotor networks after motor learning**. *J Neurosci* 2011, **31**:16907-16915.

55. Harmelech T *et al.*: **The day-after effect: long term, Hebbian-like restructuring of resting-state FMRI patterns induced by a single epoch of cortical activation**. *J Neurosci* 2013, **33**:9488-9497.

56. • Laumann TO *et al.*: **Functional system and areal organization of a highly sampled individual human brain**. *Neuron* 2015, **87**:657-670.
Description of Russ Poldrack's functional connectome, using all the resting-state functional MRI (rs-fMRI) collected on him over the span of a year. Original article describing the precise functional connectome of an individual. Revealed striking differences between individual-specific and group-averaged functional network maps.

57. Gratton C *et al.*: **Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation**. *Neuron* 2018, **98**:439-452 e5.

58. Laumann TO *et al.*: **Brain network reorganisation in an adolescent after bilateral perinatal strokes**. *Lancet Neurol* 2021, **20**:255-256.

59. Carter AR *et al.*: **Upstream dysfunction of somatomotor functional connectivity after corticospinal damage in stroke**. *Neurorehabil Neural Repair* 2012, **26**:7-19.

60. Hahamy A *et al.*: **Normalisation of brain connectivity through compensatory behaviour, despite congenital hand absence**. *eLife* 2015, **4**.

61. Makin TR *et al.*: **Deprivation-related and use-dependent plasticity go hand in hand**. *eLife* 2013, **2**:e01273.

62. Seitzman BA *et al.*: **Trait-like variants in human functional brain networks**. *Proc Natl Acad Sci U S A* 2019, **116**:22851-22861.

63. • Poldrack RA *et al.*: **Long-term neural and physiological phenotyping of a single human**. *Nat Commun* 2015, **6**:8885.
Russ Poldrack's MyConnectome study tracked the resting state functional connectivity (RSFC) organization of his brain over the course of a year, using twice weekly MRI scans. Inspired the Midnight Scan Club (MSC) and Cast-Induced Plasticity studies

64. • Gordon EM *et al.*: **Precision functional mapping of individual human brains**. *Neuron* 2017, **95**:791-807 e7.
Original Midnight Scan Club (MSC) article, describing the precise, individual-specific functional network maps of 10 volunteers. Advocated for the individual-specific Precision Functional Mapping (PFM) approach as an alternative to group-averaged brain maps. Suggested significant inter-individual variance in functional network topography and the existence of common variants.

65. Marek S *et al.*: **Spatial and temporal organization of the individual human cerebellum**. *Neuron* 2018, **100**:977-993 e7.

66. Greene DJ *et al.*: **Integrative and network-specific connectivity of the basal ganglia and thalamus defined in individuals**. *Neuron* 2020, **105**:742-758 e6.

67. Sylvester CM *et al.*: **Individual-specific functional connectivity of the amygdala: a substrate for precision psychiatry**. *Proc Natl Acad Sci U S A* 2020, **117**:3808-3818.

68. Zheng A *et al.*: **Parallel hippocampal-parietal circuits for self- and goal-oriented processing**. *bioRxiv* 2020.

69. Gordon EM *et al.*: **Human fronto-striatal connectivity is organized into discrete functional subnetworks**. *bioRxiv* 2021. 2021.04.12.439415.

70. Bergmann E *et al.*: **Individual variability in functional connectivity architecture of the mouse brain**. *Commun Biol* 2020, **3**:738.

71. Braga RM, Buckner RL: **Parallel interdigitated distributed networks within the individual estimated by intrinsic functional connectivity**. *Neuron* 2017, **95**:457-471 e5.

72. Gordon EM *et al.*: **Default-mode network streams for coupling to language and control systems**. *Proc Natl Acad Sci U S A* 2020, **117**:17308-17319.

73. Pritschet L *et al.*: **Functional reorganization of brain networks across the human menstrual cycle**. *Neuroimage* 2020, **220**:117091.

74. Rosenberg MD *et al.*: **Functional connectivity predicts changes in attention observed across minutes, days, and months**. *Proc Natl Acad Sci U S A* 2020, **117**:3797-3807.

75. Harmelech T, Malach R: **Neurocognitive biases and the patterns of spontaneous correlations in the human cortex**. *Trends Cogn Sci* 2013, **17**:606-615.

76. Guerra-Carrillo B, Mackey AP, Bunge SA: **Resting-state fMRI: a window into human brain plasticity**. *Neuroscientist* 2014, **20**:522-533.

77. Marek S *et al.*: **Towards reproducible brain-wide assoication studies**. *bioRxiv* 2020.

78. Gainey MA, Aman JW, Feldman DE: **Rapid disinhibition by adjustment of PV intrinsic excitability during whisker map plasticity in mouse S1**. *J Neurosci* 2018, **38**:4749-4761.