Tracking plasticity of individual human brains
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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.

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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
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 results 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 ventralateral premotor region (Brodmann Area 44) and the primary visual cortex [52]. These and similar studies [53–55] all reported small changes in FC (Δr ~ 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 (Δr ~ 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 [73,63,73,74].

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 [74]. 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-cast 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...
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<sub>uc</sub>) and the homotopic region of the opposite hemisphere (R-SM1<sub>uc</sub>). 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<sub>uc</sub> and R-SM1<sub>uc</sub> 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<sub>uc</sub> disconnected not only from R-SM1<sub>uc</sub>, but also from the remainder of the somatomotor network [7**].

L-SM1<sub>uc</sub> 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,
Spontaneous activity pulses in disused circuits.
(a) Resting-state functional MRI (rs-fMRI) signals recorded from left and right primary somatomotor cortex (L-SM1 and R-SM1) during the casting period. Several large pulses of spontaneous activity occur in the disused L-SM1. (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).

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 27 days after cast removal.

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 (Δr ~ 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 pathway 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.

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References and recommended reading

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

- of special interest
- of outstanding interest

   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.
   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.


26. Detailed examination of retinal waves in vivo in the developing mouse visual system. Voltage-sensitve dyes and genetically encoded calcium indicators allow first-ever demonstration that retinal waves propagate through multiple cortical and subcortical visual regions.


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.


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.


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.


