BRAIN
REVIEW ARTICLE

Functional connectivity drives stroke recovery: shifting the paradigm from correlation to causation

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Stroke is a leading cause of disability, with deficits encompassing multiple functional domains. The heterogeneity underlying stroke poses significant challenges in the prediction of post-stroke recovery, prompting the development of neuroimaging-based biomarkers. Structural neuroimaging measurements, particularly those reflecting corticospinal tract injury, are well-documented in the literature as potential biomarker candidates of post-stroke motor recovery. Consistent with the view of stroke as a 'circuitopathy', functional neuroimaging measures probing functional connectivity may also prove informative in post-stroke recovery. An important step in the development of biomarkers based on functional neural network connectivity is the establishment of causality between connectivity and post-stroke recovery. Current evidence predominantly involves statistical correlations between connectivity measures and post-stroke behavioural status, either cross-sectionally or serially over time. However, the advancement of functional connectivity application in stroke depends on devising experiments that infer causality. In 1965, Sir Austin Bradford Hill introduced nine viewpoints to consider when determining the causality of an association: (i) strength; (ii) consistency; (iii) specificity; (iv) temporality; (v) biological gradient; (vi) plausibility; (vii) coherence; (viii) experiment; and (ix) analogy. Collectively referred to as the Bradford Hill Criteria, these points have been widely adopted in epidemiology. In this review, we assert the value of implementing Bradford Hill's framework to stroke rehabilitation and neuroimaging. We focus on the role of neural network connectivity measurements acquired from task-oriented and resting-state functional MRI, EEG, magnetoencephalography and functional near-infrared spectroscopy in describing and predicting post-stroke behavioural status and recovery. We also identify research opportunities within each Bradford Hill tenet to shift the experimental paradigm from correlation to causation.

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Abbreviations: CST = corticospinal tract; DTI = diffusion tensor imaging; fNIRS = functional near-infrared spectroscopy; M1 = primary motor cortex; rTMS = repetitive transcranial magnetic stimulation; SMA = supplementary motor area

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Introduction

Stroke is a heterogeneous disease characterized by injury varying in size and location. It presents with a vast spectrum of clinical phenotypes reflecting deficits in one or more functional domains. Accurate prediction of post-stroke recovery outcome and treatment response would benefit both clinical and research settings by promoting efficient delivery of rehabilitative care and subject stratification in clinical trials. Demographic and clinical variables have shown relevance in post-stroke outcome prediction,[1] however, more recent work has focused on the predictive performance of brain-based measurements acquired from neuroimaging. Following a stroke, the brain progresses from a site of injury to a zone of enriched plasticity that is an ideal target for restorative therapies. Measurements that assess the structure and function of the brain may provide insight to an individual's recovery and capacity for therapeutic responsiveness beyond what demographic variables and clinical assessments alone convey.

The application of neuroimaging to stroke rehabilitation has led to the development of biomarkers, defined as measurements representing underlying cellular and molecular events that show associations with clinical status or its evolution.[2,3] Biomarkers may serve as surrogate measures in a clinical trial by complementing what is learned from a clinical end point.[4] Structural neuroimaging measurements, particularly those reflecting corticospinal tract (CST) injury, are well-documented in the literature as potential biomarker candidates of spontaneous motor recovery after stroke[5,6] and treatment-induced motor gains.[7,8] Consistent with the view of stroke as a 'circuitopathy',[9] functional neuroimaging measures probing neural network connectivity may also prove informative in post-stroke recovery, but further study is warranted to confirm the utility of such measurements as stroke biomarkers.

An important step in the development of biomarkers based on functional connectivity is the establishment of causality between connectivity and post-stroke recovery, e.g. *post hoc ergo propter hoc*. Current evidence predominantly consists of statistical correlations between connectivity measures and post-stroke behavioural status, either cross-sectionally or serially over time. As Fleming and DeMets assert, 'A correlate does not a surrogate make', and so declaring the validity of biomarkers based solely on correlations with behaviour is insufficient.[4]

In an ideal clinical trial setting, a single causal pathway exists between the disease and clinical end point (Fig. 1A). It is along this pathway where the intervention under investigation exerts influence over the clinical end point and where an ideal surrogate measure resides.[4] A similar scenario applies to development of stroke recovery biomarkers. In an optimal setting for such biomarker development, the causal pathway links neuroplasticity with recovery (Fig. 1B). A host of endogenous mechanisms occurring spontaneously following stroke or administration of a post-stroke restorative therapy drive neuroplasticity. A valid stroke recovery biomarker captures relevant neuroplasticity that contributes to recovery. It is important to note, however, that the two circumstances illustrated in (Fig. 1A and B) may be ideal and so overly simplistic. Several causal pathways may exist between the disease and clinical end point, and the intervention under investigation may act through a pathway that does not coincide with the surrogate measure. The complex interplay between clinical phenotypes, neuroplasticity, interventions and assessments[10] in stroke rehabilitation presents several challenges when attempting to confirm whether an association is causal or spurious.

At the inaugural meeting of the Section of Occupational Medicine in 1965, Sir Austin Bradford Hill[11] introduced nine viewpoints to consider when determining the causality of an association: (i) strength; (ii) consistency; (iii) specificity; (iv) temporality; (v) biological gradient; (vi) plausibility; (vii) coherence; (viii) experiment; and (ix) analogy. Collectively referred to as the Bradford Hill Criteria, these points have been widely adopted in epidemiology.[12] Hill's intention was not to present a checklist of rules but rather 'features to be specially considered' before concluding a cause-and-effect relationship. Rather than provide a formal systematic review of the functional connectivity literature in stroke, as there are several high-quality examples elsewhere,[13–16] our intention was to assess the role of causality between functional connectivity and stroke recovery according to Bradford Hill's tenets (Table 1). In this review, we assert the value of implementing Bradford Hill's framework in stroke rehabilitation with specific focus on the role neural network connectivity measurements acquired from task-oriented and resting-state functional MRI, EEG, functional near-infrared spectroscopy (fNIRS), magnetoencephalography (MEG) and PET in describing and predicting post-stroke behaviour and recovery. Although a significant portion of this review references sensorimotor recovery, consistent with the breadth of neuroimaging literature in this functional domain, we have expanded on the role of functional connectivity in stroke recovery to include cognitive, language, visual and proprioceptive domains. We have also considered spontaneous and treatment-induced recovery together; however, we acknowledge that some underlying mechanisms may differ between these processes. A secondary objective of this review is to identify research opportunities within each Bradford Hill tenet to shift the experimental paradigm from association to causation.

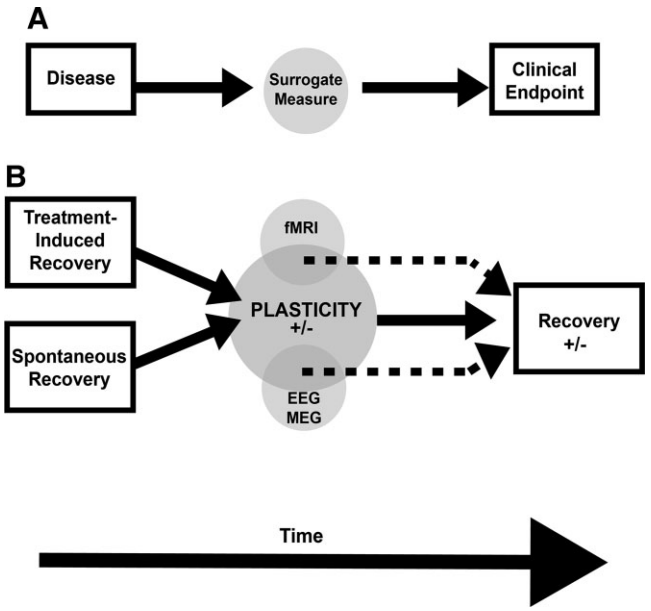

Figure 1 Neuroimaging biomarker placement on the causal pathway. (**A**) In ideal circumstances, the surrogate measure resides in the causal pathway capturing relevant disease processes represented by the clinical end point. (**B**) Potential stroke biomarkers derived from functional MRI (fMRI), EEG and MEG reflect underlying plasticity events occurring during spontaneous and/or treatment-induced recovery that positively or negatively affect stroke recovery outcomes. Figure adapted from Fleming and DeMets.[4]

Strength

Bradford Hill's first tenet refers to the association strength between two variables, typically involving the exposure to an occupational

Table 1 Bradford Hill's tenets applied to functional connectivity research in stroke

Tenet	Support for causal association between connectivity and behaviour/recovery
Strength	Larger association between connectivity and post-stroke behaviour/recovery
Consistency	Association observed across different stroke populations, settings, neuroimaging modalities, etc.
Specificity	Distinct associations (neural networks and/or connectivity patterns) according to post-stroke functional deficit(s), baseline status, recovery timeframe and lesion-related damage
Temporality	Changes in connectivity precede behavioural recovery
Biological gradient	Presence of a dose-response relationship between connectivity strength and/or magnitude of change with behavioural status and/or behavioural recovery
Plausibility	Association explained by current biological knowledge, i.e. brain physiology, anatomy, structural connectivity, etc.
Coherence	Association does not conflict with current knowledge, e.g. biology of stroke, stroke recovery, etc.
Experiment	Association based on experimental manipulation, e.g. pharmacology, neuromodulation, robotics, feedback, etc.
Analogy	A similar association in an analogous stroke setting exists

hazard and health outcome. Hill provided the compelling example between cigarette consumption and an exponential increase in lung cancer death rate between heavy smokers and non-smokers.[11] Straightforward cause-and-effect presentations such as this are rarely encountered in medicine given the multifaceted nature of disease. This applies not only in stroke but also in stroke recovery where factors such as genetics, age, pre-stroke level of function and lesion location contribute to recovery potential. An appropriate first step towards understanding the influence of functional connectivity measurements in post-stroke motor recovery is examination of the strength of association between connectivity and behaviour across diverse stroke populations. Correlation coefficients equal to or greater than 0.75 typically denote strong associations.[17] In his address, Hill also acknowledged the importance of fair to moderate associations in medicine with values ranging from 0.25–0.50 and 0.51–0.74,[17] respectively. However, we advise caution when applying this tenet to assess causality between functional connectivity and stroke recovery. A universal challenge in the neuroimaging field is statistical power,[18] and this is especially problematic in clinical neuroimaging where sample sizes frequently entail 10–20 participants. Small sample sizes are particularly vulnerable to outliers[19] and effect size inflation[20] and may not accurately represent the population effect size. It is also relevant to note the continued presence of spurious or 'voodoo' correlations,[21] and inconsistent handling of covariates, e.g. age, time post-stroke, baseline status or severity, sex, lesion volume etc., exacerbate this issue. While criticism of effect sizes and correlation coefficients is fair, it does not detract from the reported observations that some associations are strong versus weak, or consistently strong.

Plausible stroke recovery biomarkers for a given functional domain when acquired shortly after the onset of stroke, should (i) predict behavioural recovery of that function; (ii) relate to behavioural status at a given time point; and (iii) depict parallel changes with behaviour. For instance, motor system functional connectivity measurements should predict and/or correlate with motor status and motor recovery just as language system functional connectivity measurements should predict and/or correlate with language status and language recovery. Biomarkers developed from functional neuroimaging should therefore capture relevant biological events or factors promoting spontaneous and/or treatment-induced recovery. While we present a set of motor system-forward examples next to substantiate this tenet, these discussion points pertain broadly across the brain and generalize to other systems. We recognize, however, that findings might vary across functional networks probably dependant on their organization (degree of lateralization, for example) in the normal state.[22]

Task-oriented functional MRI studies in stroke describe a set of neural events that correspond to both spontaneous and treatment-induced recovery. These events, representing both compensation and restitution of motor function, encompass modulations in local[23–27] and distant[28–31] cortical and subcortical activity, changes in the interactions between hemispheres[29,32–35] and shifts in cortical representational maps.[22,36,37] A resurgence of ipsilesional and perilesional blood oxygen level-dependent (BOLD) signal activity positively relates to the recovery of motor function with coefficients ranging from 0.62–0.94.[23–27] Depending on the severity of stroke or magnitude of CST injury, activity upregulation or enhanced excitability in the contralesional hemisphere demonstrates moderate[28] to strong[30,38] associations with motor status and recovery outcomes, with stronger associations frequently observed in cases where contralesional hemisphere activity negatively correlates with improvement. Relatedly, laterality index changes signifying greater recruitment of ipsilesional relative to contralesional neural substrates[29,32–35] during voluntary movement of the affected upper extremity demonstrate fair to moderate positive associations with motor recovery. Moderate associations also exist between favourable motor outcomes and the preservation of motor map area, by functional MRI, with greater motor function correlating with a larger hand map area[36]—a finding corroborated by the relationship between transcranial magnetic stimulation (TMS) hand map area and hand function.[39]

More recent work suggests that modulations in functional connectivity are additional recovery mechanisms. Cross-sectional studies predominate the literature and demonstrate moderate to strong associations between functional connectivity measures and motor status after stroke (upper extremity Fugl–Meyer, Motricity Index, Chedoke–McMaster Stroke Assessment, $r = 0.58$–0.76, $n = 8$–55).[40–45] Longitudinal studies have found that baseline functional connectivity measures have strong associations with motor status at later time points[24,46] and also fair to strong associations with motor recovery (motor status change) over time ($r = 0.32$–0.79).[47–50] Longitudinal work also demonstrates strong associations between changes in functional connectivity and motor recovery.[51] Functional connectivity work focusing on the prediction of post-stroke cognitive function at 36 months post-stroke has also demonstrated fair to strong relationships (memory, $r^2 = 0.67$; attention, $r^2 = 0.73$; visuospatial function, $r^2 = 0.55$; language, $r^2 = 0.48$, $n = 72$).[52] Across the literature, interhemispheric connections demonstrate the strongest associations, both negative and positive, with motor status and recovery ($r = -0.70$, $r = 0.59$–0.92),[46,51,53] and also in functional domains of somatosensation (light touch, $r = 0.55$; stereognosis, $r = 0.64$, $n = 19$),[54] neglect (Bells test, $r = 0.75$, $n = 30$)[55] and memory (reaction time, $r = -0.57$; accuracy, $r = -0.67$, $n = 13$).[56]

Few studies have reported weak or absent associations between connectivity and motor recovery[57] and motor status,[58,59] which may partially reflect a publication bias. When reported, researchers described weaker predictive performance of functional connectivity measurements with increasing recovery timeframes.[57] Also, functional connectivity measures demonstrate stronger associations with non-motor post-stroke impairments, such as visual neglect[58] or memory,[60] than with motor impairments, with the latter better predicted by lesion topography.[60]

Since the inception of the Hill's viewpoints, statistical approaches for analysing scientific data have increased in sophistication. The implementation of machine learning, Bayesian statistics, advanced regression techniques and models combined with large open-source neuroimaging have enhanced the capability to assess and interpret complex datasets. Assessing the strength of an empirical association is an appropriate first step, but elucidating causality among functional connectivity and post-stroke behavioural status and recovery necessitates the consideration of Hill's other tenets.

Consistency

Consistency refers to the repeatability of an association across different populations, time points, experimental methods and physical locations. Hill reported that nearly 40 publications comprising both retrospective and prospective studies concluded similar findings between smoking and lung cancer mortality rate.[11] We define consistency by the following criteria: (i) repeatability of findings, e.g. regions of interest/nodes, connections, patterns of connectivity, etc., between resting-state and task-oriented neuroimaging; and (ii) repeatability of findings across studies using varying neuroimaging methodology. Across the task-oriented functional MRI literature, for instance, work has shown consistent patterns of cortical activation associated with optimal motor performance and recovery,[61] regardless of differences between study parameters and stroke cohorts. As we discuss in greater detail next, the most consistent functional connectivity finding in both animal and human stroke are alterations in interhemispheric connections involving homotopic regions.[14]

An increasing number of studies involving resting-state functional MRI, EEG, PET and fNIRS connectivity measurements have demonstrated the relevance of interhemispheric connectivity in stroke recovery,[7,46,51,53,62–67] complementing previous task-oriented functional MRI work.[29,32,34,35] Across studies, many have reported diminished connectivity between ipsi- and contralesional primary sensorimotor cortices early after stroke[46,63,68] that later increased over time with motor recovery.[7,46,53,63,65,68] Similar findings of disordered connectivity early post-stroke that normalizes with time and/or treatment have also been observed with aphasia[69,70] and hemispatial neglect.[71,72] These studies also show consistencies with the motor literature with regards to the lateralization of behaviour, injury and connectivity. Normal language comprehension in controls, for example, was characterized by functional connections involving left anterolateral superior temporal, basal temporal and inferior frontal regions; these connections were disrupted in those with aphasic stroke to an extent that correlated with degree of functional recovery.[69]

Akin to previous task-oriented functional MRI work that underscored the importance of perilesional activation in affected upper-extremity recovery, connectivity work also highlights the relevance of ipsilesional primary motor cortex (M1) connectivity in recovery. Preliminary connectivity work also suggests different network connectivity patterns following stroke based on severity,[68,73] type of stroke[7] and magnitude of white matter injury[74] that align with past task-oriented functional MRI work demonstrating greater bilateral recruitment of contralesional and secondary motor regions in those with increasing severity and extent of injury and in those with poor behavioural outcomes.

Hill's consistency viewpoint implies a causal relationship as universal and independent, meaning that a causal relationship persists under varying experimental settings and circumstances and is observed independently across investigators. One may argue that inconsistencies of findings across studies may reflect differences in the stroke population studied or in experimental methods such as task difficulty (when task-oriented) or data acquisition details. This assertion is probably true to some degree; however, differences in study findings might also arise from an incomplete relationship between brain plasticity and a given neuroimaging measure such as connectivity. This may explain why several have found predictive models containing both structural and functional neuroimaging measures to perform better than models containing either measure alone.[7,48] Hill's consistency viewpoint calls attention to rigour and reproducibility and underscores the value of reporting and publishing negative findings. Incorporating Hill's consistency viewpoint in future work might at times therefore suggest incorporating additional statistical analyses, e.g. cross-validation and bootstrapping, in the study design to emphasize validation.

Specificity

The specificity tenet implies a greater probability of causality when the exposure variable relates to a single outcome.[11] Hill reported that under causal circumstances, exposure alone is responsible for the onset of a condition. However, with the evolution of science and technology, including neuroimaging, comes a more comprehensive understanding of disease. Today, we recognize that a given health-related outcome may reflect multiple causes and confounding variables. Another interpretation of Hill's specificity tenet is that a causal association is likely if the association is present in a certain population. Bradford Hill referred to a population of smokers, recognizing the strength of association between smoking and lung cancer death rate.[11] Here, a 'certain population' refers to a certain stroke subgroup as defined by stroke involvement (cortical/subcortical versus subcortical), chronicity (acute versus subacute versus chronic), or initial impairment or functional status, for example. Extrapolating this tenet to stroke connectivity research means that functional connections might vary in relevancy to behaviour according to stroke subgroup. Indeed, researchers have identified distinct patterns of functional connectivity in those with complete versus partial hand paralysis after stroke.[75,76] These findings align with similar findings observed in the functional domain of speech production.[77] Following a comparison of individuals with and without apraxia of speech post-stroke, investigators found that those with apraxia demonstrated reduced connectivity between bilateral premotor cortices relative to those without apraxia and that reduced connectivity correlated with the severity of apraxia.[77] Together, this work demonstrates that the weight or importance of certain neural network connections specifically varies according to the magnitude and type of deficit.

As certain patterns of functional connectivity are specific to certain clinical phenotypes and outcomes, future work should begin to categorize patterns of functional connectivity as either adaptive or

maladaptive based on principles of restitution and compensation, respectively. For instance, studies of effective connectivity have shown that contralesional M1 exerts a positive influence over ipsilesional M1 during early post-stroke recovery[78,79] but a more maladaptive role during later recovery. Preliminary work in individuals with chronic stroke that sustained lesion-related damage in the vicinity of the internal capsule found significant negative associations between CST integrity and M1–M1 functional connectivity.[45] The authors surmised that enhanced interhemispheric functional connectivity may partially reflect upstream compensatory activity following downstream CST damage.[45] These findings complement more recent work by Hordacre *et al.*[80] where individuals with chronic stroke displaying ipsilesional motor evoked potentials displayed greater interhemispheric sensorimotor coherence in the beta frequency range compared to those with absent ipsilesional motor evoked potential responses that positively correlated with upper limb motor status. Combined, this work demonstrates the impact of motor-specific anatomical substrate damage on upstream motor neural network functional connectivity. Work by Carter *et al.*[53] and Baldassarre *et al.*[71] also showed abnormal interhemispheric functional connectivity patterns within dorsal attention and motor networks that correlated with the degree of domain-specific deficit. More recent work has revealed alterations in sensorimotor network connectivity exclusively in those with impaired touch sensation[81] and have demonstrated regional specificity of graph theoretical measures in the beta frequency band according to motor and language recovery.[82]

These findings also illustrate specificity as it pertains to network specialization–domain-specific behavioural deficits accompanied by alterations in connectivity in cortical regions that functionally correspond with that domain. Establishing causality between specific neural circuits and behaviour holds exciting clinical potential including the expansion of precision medicine to neurorehabilitation.[83] Findings by Zhou *et al.*[84] exhibit how specific circuits might also enhance the prediction of treatment-related gains. Following a course of visuomotor tracking training with the paretic upper extremity in subjects with chronic stroke, Zhou and colleagues[84] observed that activity in the high beta frequency range (20–30 Hz) between electrodes overlying ipsilesional M1 and ipsilesional parietal cortex significantly predicted improvement in a motor tracking task. Predictive performance of EEG coherence was circuit-specific, as ipsilesional M1 coherence measures involving leads overlying other areas (contralesional parietal cortex or M1; or ipsilesional premotor, prefrontal or visual cortices) did not significantly predict tracking gains. An important feature of this work that further supported circuit specificity was the use of a negative control (ipsilesional M1 coherence with ipsilesional visual cortex). Future work addressing specificity-related questions or hypotheses would benefit from the inclusion of similar negative controls that involve either a circuit or a network that is functionally distinct from the behavioural task or operation under study.

Use of multiple neuroimaging modalities may also provide additional evidence of circuit or network-level specificity. Combining functional neuroimaging and electrophysiological information imparted by EEG enabled Mantini *et al.*[85] to characterize six resting-state networks by their distinctive electrophysiological signatures. This work elucidated the biological and physiological attributes of spontaneous resting-state activity and also demonstrated frequency-specific oscillatory properties for each resting-state network, consistent with the notion of neuronal oscillations subserving behavioural processes.[86–90] Thus, consideration of Hill's specificity tenet also extends to the specific neurophysiological properties of a neural network or connection.

Temporality

Hill[11] also discussed the aspect of temporality in causal associations stating that the associated factor or event must occur before the health outcome of interest. Today, we not only conceptualize temporality as cause preceding the effect but also as cause predicting the effect.

There are several temporal features that strengthen the causality argument between functional connectivity and recovery. In line with Hill's original explanation, observing a connectivity pattern associated with a positive outcome that is present before but not after recovery suggests the presence of biological change early following stroke that sets the stage for subsequent recovery. It also refutes the reverse—improved outcomes drive changes in connectivity. Animal stroke models, particularly those in rodents, demonstrating histological and cellular changes,[91–93] angiogenesis[94] and altered astrocyte reactivity[95] shortly after stroke provide proof of principle that some forms of plasticity precede functional recovery. These regenerative events may further facilitate neurogenesis[96] and the formation of new connections.[97,98]

Most of the work depicting changes in functional connectivity preceding behavioural change exists outside of stroke. Klingner and colleagues[99] acquired 10 resting-state functional MRI scans from one individual beginning at the onset of Bell palsy (right-sided facial palsy) and ending at complete clinical recovery. During this time, investigators observed increases in functional connectivity between left M1 and a facial motor network (bilateral cerebellum and inferior ventral precentral gyri) before clinical improvement.[99] Others have observed disordered functional connectivity before the development of dementia in Parkinson's disease[100] and the onset of symptoms in Huntington's disease.[101] In stroke, the most convincing evidence of connectivity preceding behavioural recovery comes from work by Park and colleagues[46] that found that changes in connectivity occurring during early post-stroke timeframes contributed to later behavioural recovery. The intricacy of post-stroke brain reorganization that Allred *et al.*[102] describes as a 'multiphasic process interacting with glial and vascular changes', might partially explain the lack of evidence in stroke, relative to other areas of medicine, depicting functional connectivity preceding recovery. Post-stroke brain reorganization is also driven by the timing, type and dose of post-stroke training,[103] which present additional challenges when attempting to capture the onset of brain plasticity mechanisms, i.e. neuronal network alterations, that subserve and precede behavioural recovery. Most of the evidence supporting this tenet comes from work showing changes in functional connectivity over time that coincide with, but do not follow, recovery and also from work demonstrating significant prediction of recovery outcomes from connectivity measures acquired during an earlier time point.

As past work has shown that most motor recovery occurs during the first 3 months post-stroke,[104–106] the steepest portion of the slope depicting functional connectivity change would coincide with post-stroke months 0–3. Findings from task-oriented functional MRI and EEG work reinforce these inferences. In a longitudinal study spanning 12 months with serial task fMRIs comprising active and passive finger and wrist flexion and extension, Tombari *et al.*[107] identified changes in neural activation between the subacute and chronic phases of post-stroke motor recovery:

from 20 days to 4 months post-stroke, subjects demonstrated a contralesional to ipsilesional shift in sensorimotor cortex hyperactivation that paralleled motor recovery and that later stabilized between months 4–12 post-stroke coinciding with a normalization of ipsilesional sensorimotor activation compared to controls. Longitudinal EEG studies examining event-related synchronization and desynchronization of cortical oscillations have shown the resurgence of premovement delta[108,109] and beta[50] oscillations that occurred in parallel with changes in motor behavioural recovery.

A growing number of longitudinal resting-state functional MRI,[46,62,63,68,78,110] fNIRS[111] and EEG/MEG[41,51,112] connectivity studies involving alpha, beta and delta frequencies, revealed similar temporal features whereby disordered connectivity observed during the acute or subacute phases post-stroke (<24 h to 1 month) later normalize to resemble healthy controls by 3–12 months post-stroke. Similar findings exist in the recovery of somatosensory[113] and cognitive function[114] with the latter study showing a strengthening of connections within the default mode network by three months post-stroke that correlated with cognitive recovery. Examination of graph theory measurements has shown changes in network topography concurrent with behavioural recovery. Increased centrality in ipsilesional M1 and contralesional cerebellar regions during recovery, for instance, suggests increasing importance of these nodes in the defined network.[63] Others have detected stroke-induced alterations in local specialization, integration and small-worldness,[42,115–117] but additional work is needed to gain perspective on how these measures change with time, treatment and recovery. Recent work using dynamic resting-state functional MRI via a sliding window to increase temporal resolution from minutes to seconds found multiple transitory connectivity patterns within the motor-related networks based on motor impairment severity in those with acute ischaemic stroke.[118] The extent to which these transient connectivity patterns shape ensuing motor behavioural recovery and influence other neural network change deserves further study.

Another temporal attribute in connectivity research is that connectivity is an effective predictor of motor recovery when the measure is temporally linked with the recovery measure. One would therefore anticipate higher r^2 values resulting from models where the timeframe of recovery occurs in close succession to the connectivity assessment and lower r^2 values from models predicting a timeframe more remote (months to years) from the connectivity assessment. In support of this belief, neuroimaging scans acquired shortly after stroke predict motor recovery typically spanning a period of 3–6 months from the initial scan/recording,[78,117] inferring that the baseline scan has predictive value because it captures biological events that occur soon after the scan and thus support behavioural recovery. Work by Lin *et al.*[57] showing significant predictive power of motor status at 1–2 weeks and 3-months post-stroke but not 12-months from homotopic sensorimotor network connectivity provides additional support as does recently published work by Vicentini and colleagues[119] showing correlations between subacute default and salience network connectivity and cognitive recovery at 6 months post-stroke. Similarly, connectivity measures may also demonstrate optimal predictive performance when collected immediately before the commencement of a behavioural therapy or treatment. Wu *et al.*[48] found that a measure of EEG coherence acquired at baseline, before a 28-day upper-extremity rehabilitation regimen, significantly predicted pre-/post-changes in motor impairment scores (cross-validated $r^2 = 0.79$). Recent work implementing more data-driven regression approaches for post-stroke recovery prediction have also demonstrated the utility of functional connectivity measures in predicting early motor recovery across inpatient rehabilitation hospitalization ($r^2 = 0.62$)[120] as well as memory, attention, language and visuospatial function at 36 months post-stroke ($r^2 = 0.43$ to 0.73).[52]

In addition to machine learning, support of temporality underlying functional connectivity in stroke will come from studies incorporating multiple imaging sessions before the start of an intervention or from staggering the timing of interventions among subjects to show that the image most closely linked temporally to the intervention will display the strongest prediction power. The value of serial neuroimaging during an interventional study is exemplified by Dong *et al.*[121] that examined changes in brain activation in subjects receiving 2 weeks of constraint-induced movement therapy and found that task-oriented neuroimaging measures acquired during treatment correlated with post-therapeutic changes in motor function and pre-post motor function gains; similar studies are needed using connectivity measures. A crossover study design with scanning done at each interval is another potential approach. Here, there would be an anticipated delay between the 'cause' and the expected effect; focusing on forms of neural plasticity that occur relatively soon after an intervention, the observed imaging-based effect would occur shortly after that delay. Future work also requires sufficient resolution to parse temporal aspects of neuroplasticity related to recovery at both group and individual levels.

Still, others have approached stroke recovery prediction using time as a model variable to address the time-sensitive nature of brain reorganization and connection properties.[122] By adopting a temporal exponential random graph model approach to longitudinal network analysis in stroke, Obando and colleagues[122] found that time-varying ipsilesional intrahemispheric and interhemispheric connections in the subacute phase of stroke recovery predicted language and visual recovery outcomes at 12 months post-stroke. Importantly, other statistical modelling procedures that did not account for the time-dependent nature of neural network remodelling post-stroke failed to yield similar predictive findings. Future modelling strategies might therefore treat time as a model variable.

Biological gradient

The presence of a biological gradient or a dose-response relationship between neural connectivity and behaviour provides further support of causality. For instance, greater connectivity strength or an abundance of certain connectivity patterns would yield more favourable outcomes as indicated by greater behavioural change over time or following treatment.[40,68,82,123–125] Conversely, the absence of a biological gradient implies that functional connectivity strength involving certain regions or networks does not subserve the behaviour or behavioural change under study. Three distinct biological gradients emerge in the literature: (i) cross-sectional gradients; (ii) future (prediction) gradients; and (iii) parallel gradients whereby change in functional connectivity coincides with change in behaviour.

Examples of these gradients in the literature frequently involve connectivity with ipsilesional M1. For instance, Wu and colleagues[48] observed a significant association between EEG leads overlying ipsilesional M1 with post-stroke motor status (cross-sectional gradient), and later observed significant associations between motor gains across a 28-day upper-extremity rehabilitation program with increased beta (20–30 Hz) coherence between ipsilesional M1 and premotor regions and decreased connectivity between ipsilesional M1 and parietal regions (parallel gradients). Relatedly,

Nicolo *et al.*[82] reported positive associations between whole brain connectivity with EEG leads overlying ipsilesional M1 in the beta frequency range at 2–3 weeks post-stroke and motor recovery outcomes at 3 months, thus illustrating the positive implications of the resumption (or strengthening) of connections involving ipsilesional M1 on motor status and recovery. Importantly, Nicolo *et al.*[82] also showed that delayed increases in whole brain connectivity with ipsilesional M1 in the beta frequency range during this timeframe negatively correlated with clinical recovery during this time. Others have found shifts in interhemispheric coupling between M1 regions[78,79,124] that correlated with motor status at both early and late recovery time points and also with the degree of motor recovery.[48,51,53,63,74] Relatedly, Olafson and colleagues[126] longitudinally studied functional connectivity patterns in 23 individuals with ischaemic pontine stroke from 1 week to 6 months post-stroke. The extent of functional connectivity reorganization related to both the magnitude of structural and functional connectome damage and also to the magnitude of motor recovery. Individuals with greater baseline motor impairment demonstrated greater functional connectivity reorganization during the 1–2-week post-stroke timeframe, which positively correlated with motor recovery at 6 months (prediction gradient).

Biological gradients also exist in the domains of post-stroke somatosensation,[54,113] language,[127] apraxia[128] and neglect.[129,130] For example, relative to individuals with mild to moderate somatosensory impairment at approximately 6 days post-stroke, individuals with severe somatosensory impairment around this timeframe depicted reduced interhemispheric and ipsilesional intrahemispheric somatosensory network connectivity involving bilateral primary sensorimotor cortices, supplementary motor area (SMA), insula, cerebellum and inferior and superior parietal regions.[54] Reduced interhemispheric and ipsilesional intrahemispheric somatosensory network connectivity negatively correlated with an individual's perceptual threshold of touch; whereas, enhanced interhemispheric connectivity positively correlated to stereognosis and light touch assessments.[54] Similarly, across individuals with more severe speech comprehension impairments resulting from left hemisphere stroke, MEG analyses revealed stronger interhemispheric connections between bilateral superior temporal gyri following phonological training that coincided with improvement in speech comprehension.[127] These examples of cross-sectional and parallel biological gradients suggest a scaling of connectivity with post-stroke behavioural deficit and training-induced recovery, respectively.

The absence of a biological gradient between a measure of functional connectivity and post-stroke behaviour or recovery may partially explain the few negative findings among the stroke neuroimaging literature. Several have concluded that predictive models containing a combination of clinical variables and CST integrity[57] or lesion topagraphy[60] better predict motor status and recovery. In the latter study, the authors surmised that the wider distribution of neural networks, characteristic of more associative domain of function such as attention and memory, may account for why functional connectivity demonstrated better predictive performance in these domains compared to the sensorimotor domain characterized by a highly localized (high degree of within-network connectivity) neural network.[60] Others examined changes in resting-state functional MRI between 5 and 26 weeks post-stroke and observed no changes in connectivity during this window despite differences in intrahemispheric connectivity among motor regions between ipsilesional and contralesional hemispheres.[131] Notably, researchers acquired this cohort from a larger clinical trial.[132] The strict enrolment criteria probably generated a homogenous sample that provided a limited gradient of brain and behavioural measurements. The author's findings of no between-group differences in connectivity measurements between patients and controls and a rather small extent of behavioural recovery (the average improvement in upper extremity Fugl–Meyer score was below the clinically meaningful cut-off) further support this notion. Additional work is needed to confirm whether this sample homogeneity contributes to a lack of prediction. as other studies reporting negative findings featured larger and more heterogeneous samples[57,60] with neuroimaging measurements procured earlier post-stroke. While seemingly contrary to the previous assertion of sample homogeneity contributing to negative findings, sample heterogeneity may also contribute to negative findings. Samples exuding more heterogeneity may also possess multiple biological gradients that ultimately reduce the statistical power needed to detect relationships of interest.

Negative findings raise the possibility that changes in circuit or network connectivity may not directly translate to behaviour. Furthermore, while stroke alters network connectivity, those underlying mechanisms involved in mediating circuit/network connectivity change towards pre-stroke levels or to normative values based on age-matched controls may be distinct from those mechanisms promoting spontaneous and treatment-induced recovery.[133] Alternatively, some changes in connectivity may be insufficient to manifest as improved behaviour, which would dampen measures of a biological gradient. These are key issues for future work to address.

Plausibility

Hill's plausibility criterion implies that a causal relationship is biologically sensible: that the proposed biological mechanisms explaining the association align with current scientific knowledge. Hill was keen to acknowledge that the breadth of knowledge at a given time may limit confirmation of biological plausibility in some instances.[11] In this tenet, we emphasize biological plausibility with respect to (i) functional connections and behaviour; and to (ii) functional connections and targeted treatments. Additional discussion of biological plausibility centres around preclinical work and emerging work investigating the relationship between structural and functional connectomes, 'connectional diaschisis'[134] and the neurochemical underpinnings of functional connectivity.

For instance, recent work by Ramage and colleagues[135] found that functional connections involving brain regions associated with semantic and phonological processing predicted language function in individuals with chronic post-stroke aphasia. Previous work summarized in the specificity tenet also exemplifies biological plausibility by showing changes in region-specific connections associated with domain-specific behavioural changes.[53,71,82] Furthermore, a treatment targeting one functional neural network should lead to behavioural improvement in that corresponding domain.[136–141]

It is also biologically plausible for networks to interact so that changes in one functional neural network induce behavioural improvement in a second functional domain. For instance, Itabashi and colleagues[142] recognized contributions to motor speech production from the left precentral gyrus in individuals with apraxia of speech following stroke. An intervention targeting a relevant motor circuit to improve motor deficits might therefore also result in improvement in speech deficits. Such network interaction

effects have not been reported widely across the literature and thus require additional study.

Plausibility also extends to work attempting to elucidate the biology underlying functional connectivity, including relationships between structural and functional connectivity. Anatomical patterns of connectivity support the existence of functional networks. Structural connectivity, as measured by diffusion tensor imaging (DTI) tractography, has shown relevance in post-stroke motor recovery, but changes in structure do not fully explain behavioural recovery. Functional changes are also important. The relationship between structural connectivity and functional connectivity is complex, which might be explained by neuroplasticity driving brain reorganization following stroke as well as the inherent organization of the brain comprising trillions of synapses. Indeed, evidence suggests that functional connectivity reflects polysynaptic anatomical connections[143,144] and common afferent and efferent connections[145] as opposed to direct synaptic connections. Findings from work using task-oriented functional MRI have shown spatial overlap of structural and functional plasticity with areas of increased cortical thickness colocalizing with areas of increased BOLD signal activity.[25] With the growing acceptance and accumulation of evidence illustrating stroke-mediated disruption of both structural and functional connetomes,[146,147] much of the ongoing work in connectivity research seeks to understand how these connectomes relate to one another (review by Damoiseaux and Greicius[148]). Many assert that structural connectivity serves as the scaffolding to functional connectivity on the basis of three lines of inquiry: (i) structural connectivity predicts functional connectivity[149–151]; (ii) the associations between behaviour and functional connectivity are predicated on underlying white matter integrity and/or the extent of stroke-related injury to white matter tracts[74]; and (iii) structural connectivity strength positively relates to functional connectivity strength.[74,152] However, some have concluded negative associations between functional and structural connectivity strength may reflect underlying compensatory neuroplasticity mechanisms following stroke,[45] while others have found no association.[43] Several factors probably explain the discrepancy in findings including timeframe post-stroke, baseline impairment status and varying methodologies used to analyse white matter integrity and functional connectivity. A next step to mitigate these incongruities is the implementation of longitudinal studies examining associations between structural and functional connectivity strength beyond CST and interhemispheric M1 connectivity.

It is important to acknowledge that findings in healthy participants have depicted functional connectivity between regions that share no direct structural connections.[150,153] An absence of structural connectivity underlying regions depicting functional connectivity may imply contributions from indirect structural connections via a third anatomical region.[143,146,148] In support of this view, work by Honey and Sporns[150] demonstrated that indirect structural connections explained variance in functional connectivity apart from the variance explained by direct structural connections. Combined work in stroke underscores the motor behavioural relevance of functional connections between dorsolateral prefrontal cortex and M1[46] potentially mediated by indirect structural connections via premotor cortex.[154] Additional work has also shown disrupted functional connectivity between M1 and cerebellum following pontine lesions[143] and also between regions that share no direct structural connections as the result of the lesion damaging the shortest structural path between these regions.[146] These collective findings encourage additional study of the influential role of indirect structural connections on functional connectivity and post-stroke recovery.

Relatedly, mounting evidence of altered functional connectivity between regions remote from the lesion has led to an expanded view of diaschisis[155] entailing 'changes in coupling between two nodes of a defined network involving areas distant from the lesion' (review by Carrera and Tononi[156]). Campo *et al.*[134] referred to this subtype of diaschisis as 'connectional diaschisis' and its existence in post-stroke memory,[157,158] executive function[159] and neglect[58,160] deficits bolsters the plausibility of the assertion that functional connectivity is causally contributory to behavioural status after stroke. An important topic that future work should address is the disentanglement of functional connectivity alterations arising from pathological mechanisms such as diaschisis from those arising from mechanisms related to spontaneous recovery in the form of neuroplastic change.[156]

Multimodal neuroimaging studies involving magnetic spectroscopy in combination with functional imaging have provided a neurochemical basis to functional connectivity. The proposed neurochemical substrates mediating changes in functional connectivity align with those involved in the neuroplasticity of learning. Several studies in healthy controls have shown associations between changes in functional connectivity during motor learning and GABA levels[161,162]; these complement other work showing GABA-A mediated facilitation in beta oscillations during movement[163] and the involvement of movement-related beta band activity in visuomotor learning prediction.[164] Whether or not these findings translate to stroke remains to be seen, but work showing relationships between diaschisis and abnormal GABAergic transmission in rodents post-stroke,[165] the involvement of GABA-A receptor function with increased tonic inhibition post-stroke and GABA subunit alteration in promoting motor recovery in mice encourage further study in human stroke.

Biological plausibility also emerges from preclinical studies. Pivotal findings from rodent[166] and non-human primate[167,168] stroke illustrating shifts in somatotopy representation and peri-infarct reorganization, for instance, align with similar findings in humans.[22,34,169,170] Here, in the context of post-stroke functional connectivity, preclinical findings also depict associations between functional and structural connectivity[171–173] that correlate with post-stroke behavioural outcomes.[174,175] Current work also indicates similar network changes between mice and humans following a stroke that involved increased connectivity in sensorimotor, frontal and cerebellar regions at 9 and 14 days post-stroke, respectively.[176] These comparable findings across species also uphold Hill's coherence tenet described in detail next.

Coherence

If plausibility is limited by current scientific knowledge, then coherence infers that a causal association does not profoundly conflict with this current state of knowledge.[11] Causal relationships between functional connectivity and stroke recovery should therefore concur with the natural history and biology of the disease.

Previous accounts of the literature in the previous temporality section, for example, suggests that the timing of optimal sensorimotor prediction via functional MRI aligns with the timing of sensorimotor recovery, and that this recovery evolves in a sensible manner with respect to behavioural evolution. Similar themes emerge from both task-oriented functional MRI and functional connectivity literature, especially those using serial scans: (i) shifts in interhemispheric balance during the period of recovery[22,107]; (ii) activation and connectivity patterns resembling healthy controls in

those individuals with stroke who experience the best behavioural outcomes[38,177]; and (iii) greater recruitment of secondary motor and contralesional networks with poorer behavioural outcomes.[24,38,177] Importantly, many of the events described in the task-oriented literature, such as changes in the laterality index, shifts in somatotopy maps and recruitment patterns, and perilesional activation emerge during a recovery timeframe similar to that of functional connectivity change.

The case for coherence is strengthened by the fact that, within the connectivity literature, there are a number of consistent observations between species and across labs, neuroimaging modalities, and processing/analysis pipelines that fit within themes of laterality and expanded network recruitment. The former refers to the clinically relevant role of interhemispheric inhibition and connectivity between ipsilesional and contralesional motor regions,[46,53,63,68,178] findings that are concordant with preclinical studies.[174,175,179] From a network perspective, stroke recovery has consistently been associated with dynamic changes in multiple networks that operate both in a functionally segregated mode and also in a more globally integrated mode. For instance, damage to the motor network produces motor behavioural deficits; however, other networks such as the attentional network also contribute to these deficits.[180,181] This is analogous to work initially highlighting the role of beta oscillations in motor function[182–184] and post-stroke recovery[48,50] and others also remarking on the importance of alpha[112,185] and delta[51,108] oscillations in post-stroke motor status and recovery. Given the role of these oscillatory frequencies in attention and cognition,[186–188] it is conceivable that these frequencies also support motor system function.

Furthermore, disruption in functional connectivity is a coherent observation across disease states apart from stroke. Other movement-related diseases, particularly those classified as neurodegenerative or inflammatory such as amyotrophic lateral sclerosis,[189] Parkinson's disease[190] and multiple sclerosis[191] also demonstrate similar changes in functional connectivity.

Experiment

Experimental manipulation, according to Hill,[11] may provide the strongest evidence of causality. Changes in motor status or recovery outcome resulting from experimental modulation of a single functional connection might shift the connectivity–behaviour relationship from correlative to causative. The application of neurostimulation and pharmacology in animals and humans, collectively, supports causality through experimentation.

From an animal perspective, recent work by Kadono and colleagues[192] applied repetitive transcranial magnetic stimulation (rTMS) to ipsilesional M1 in primates with central post-stroke pain and longitudinally studied functional connectivity. Resting-state functional MRI analyses initially revealed an abnormally strong functional connection between ipsilesional mediodorsal thalamus and amygdala. Repetitive TMS application resulted in reduced pain symptoms and functional connectivity strength between these regions. These findings of altered connectivity and improved pain symptomology lend support for Hill's tenets of experiment and specificity given the involvement of thalamus and amygdala in emotion and memory, which are relevant in pain. Interestingly, the application of rTMS to ipsilesional M1 to evoke change in connectivity strength in a deep subcortical circuit emphasizes the expansive network underlying central post-stroke pain. Stimulation to one part of the network resulted in altered connectivity to another, implying that specificity does not necessarily entail stimulation of that specific circuit but, rather, stimulation to the broader network containing the circuit. This finding raises important implications in the development of circuit-targeted therapies using non-invasive stimulation.

In healthy controls, manipulation of neural circuits and networks through pharmacology and non-invasive brain stimulation modulated functional connectivity. Early work demonstrated dose-dependent changes in resting-state functional connectivity in healthy individuals following the administration of sevoflurane anaesthesia.[193] Application of non-invasive brain stimulation involving a wide range of modalities including theta burst stimulation[194] and transcranial direct current stimulation[195] have also altered functional motor network connectivity. Here, too, investigators noted that changes in connectivity following stimulation occurred in a dose-dependent manner[194] often influencing intra- and interhemispheric sensorimotor network connections beyond the stimulation site.[195] Stimulation of the visual-attention network using inhibitory rTMS, for example, demonstrated both immediate and delayed changes in functional connectivity that were widespread.[196] A recent review by Hartwigsen and Volz[197] provides a thorough review of short-term reorganization of motor and cognitive networks using a combined rTMS-functional MRI approach.

Several pharmacological experimental examples also exist in stroke. Pharmacological enhancement of norepinephrine[198] and orexin expression[199] resulted in altered network connectivity in two double-blind placebo-controlled crossover stroke trials. In one of these studies, the administration of an antidepressant (reboxetine) in individuals with subacute and chronic stroke with mild to moderate hand paresis resulted in enhanced effective connectivity of SMA over ipsilesional M1 that correlated with improved motor performance of the ipsilesional hand.[198] In the second study, individuals with post-stroke fatigue receiving modafinil, a neurostimulant, showed changes in resting-state connectivity in left frontoparietal, somatosensory, mesolimbic and thalamic networks that concurred with improvements in self-reported measures of fatigue and quality of life.[199]

Application of rTMS in stroke has also shown changes in functional connectivity often relating to behavioural change. High-frequency (10 Hz) rTMS to dorsolateral prefrontal cortex improved cognitive function relative to sham stimulation, which related to increased functional connectivity between medial prefrontal and ventral anterior cingulate cortices.[139] Following previous work that applied low-frequency (1 Hz) rTMS to contralesional M1 and observed improved motor performance in conjunction with enhanced ipsilesional connectivity between M1 and SMA and reduced influence from contralesional M1,[140] another group randomized individuals with stroke to either high-frequency (10 Hz) rTMS to ipsilesional M1 or low-frequency (1 Hz) rTMS to contralesional M1.[141] Investigators observed distinct patterns of functional connectivity change among a predefined motor network between rTMS groups that accompanied motor improvement.[141] Combined with previous findings that observed specific changes in functional connectivity that predicted treatment effect[7] and paralleled treatment-related behavioural change according to baseline stroke severity,[200] these findings collectively highlight important experimental considerations that may affect the functional connectivity–behaviour relationship.

In addition to pharmacological and neurostimulatory routes of experimental manipulation, the delivery of visual and tactile neurofeedback through brain–computer interface technology in stroke[201–203] as well as enriched sensory environments[204] may

also serve as alternative methods for probing causality between motor behaviour and functional connectivity. Current work by Mihara and colleagues[137] showed enhanced efficacy of gait and balance-related motor imagery training with fNIRS-guided neurofeedback facilitation of SMA in individuals with subcortical stroke (>3 months post-stroke).[137] Those who received fNIRS-mediated neurofeedback demonstrated enhanced connectivity involving SMA and contralesional inferior frontal gyrus that correlated with improved balance performance. These findings suggest that neurofeedback targeting a neural network involved with motor imagery resulted in enhanced behavioural recovery.

While correlative relationships between connectivity and behaviour have enhanced our understanding of the biology of stroke recovery, using experimental methods to establish causality between connectivity and behaviour has the potential to result in a paradigm shift in rehabilitative treatments and therapies. For the field of stroke rehabilitation, implementation of a precision medicine-based treatment approach akin to other medical practices such as oncology, depends on experimental manipulation of neural circuits and networks under this Bradford Hill tenet.

Analogy

In special instances when attempting to disseminate causality, Hill[11] proposed that one may 'judge by analogy'. He acknowledged the effects of thalidomide and rubella on pregnancy and affirmed that the scientific and medical communities would probably accept weaker evidence of a similar drug or virus causing a similar effect in pregnancy.[11] Several interpretations of this tenet have surfaced over the years. Akin to Bradford Hill's example,[11] some have interpreted this tenet to mean that one can accept an additional factor as causal, despite lower quality of evidence, if that factor produces a similar effect as the previously identified causal factor.[205] Others' interpretations of analogy have led them to question scientific ingenuity, 'Whatever insight might be derived from analogy is handicapped by the inventive imagination of scientists who can find analogies everywhere. At best, analogy provides a source of more elaborate hypothesis about the associations under study; absence of such analogies only reflects lack of imagination or lack of evidence'.[206]

Our interpretation of 'judge by analogy' aligns with points made by Fedak *et al.*[12] that 'the modern value of analogy is not gained from confirming a causal inference, but rather from proposing and testing mechanistic hypotheses' and by Höfler[207] whom encouraged scientists to think about whether or not they would observe the same association under analogous experimental settings as used in other studies. Discussion of this tenet echoes prior discussion points concerning plausibility, consistency and coherence. As an amalgamation of these prior tenets, consideration of the analogy tenet should therefore prompt researchers to devise 'analogous' experimental settings using additional tools and technology to confirm whether associations between functional connectivity and post-stroke recovery endure.[12,207] This may involve the examination of associations across stroke recovery timeframes, stroke subpopulations, species, human neuroimaging modalities and data analysis methods to infer causality. We provide several examples of 'judging by analogy' next.

When examining functional connectivity broadly across stroke recovery, experimental findings depicting similarities between the biology of spontaneous recovery and treatment-induced recovery emerge. Several functional MRI,[46,62,63,68,78] EEG/MEG[41,51,112] and fNIRS[65,111] papers have shown disordered connectivity initially after stroke, including in subpopulations of stroke (aphasia and hemispatial neglect[69–72]), that normalize over time to resemble that of healthy controls. Treatment-induced recovery using pharmacology,[198,199] robotic therapy[48] and neurostimulation[139–141] have demonstrated similar phenomena by showing disordered connectivity normalizing with intervention. We want to highlight that the previously referenced literature collectively employed a variety of neuroimaging modalities, which also support 'judgement by analogy'.

The examination of Hill's analogy viewpoint across subpopulations of stroke also underscores the unique challenges in stroke research related to participant and stroke heterogeneity and the generalizability of findings. There is a need (and benefit) to conduct functional connectivity studies that reflect the broad population,[208] especially since the majority of work primarily entailed participant samples depicting narrow ranges of deficit and impairment. One recent study examined both cross-sectional and serial EEG measures of power and coherence with motor status/recovery and injury extent in a purposely heterogeneous sample.[51] Stratification of the original cohort ($n = 62$) enabled researchers to further examine these associations by time post-stroke and lesion topography before ascertaining the importance of low-frequency delta (1–3 Hz) oscillations in stroke. However, residing on the opposite end of the spectrum from sample homogeneity and limitations in generalizability is sample heterogeneity. Talelli *et al.*[209] eloquently articulates this issue, 'One of the problems in exploring correlations between recovery and TMS measures has been the mix in the size and location of patients' lesions both within and between different studies'. Judging by analogy across stroke subpopulations may therefore reconcile issues encountered in the interpretation and application of experimental findings perpetuated by sample homogeneity and heterogeneity.

In addition to judging by analogy across subpopulations of stroke, 'judging by analogy' across species also strengthens the causality argument between functional connectivity and post-stroke behaviour. Apart from those preclinical studies previously discussed, animal work involving temporally precise manipulation of specific neural circuits using optogenetics (reviewed by Cheng *et al.*[210]) has provided findings concordant with MRI and post-stroke connectivity work. Lim and colleagues[211] observed 'connectional diaschisis' in mice at 1-week post-stroke that significantly resolved by 8-weeks post-stroke. These network-wide findings compliment previous non-human primate work showing changes in functional connectivity following middle cerebral artery stroke expanding beyond the affected sensorimotor region.[212] Optical imaging experiments in mice have also revealed novel structural and functional circuitry accompanying sensory remapping during stroke recovery[98] and the recovery of structural and functional network properties to pre-stroke status following a combined robotic and pharmacological rehabilitation paradigm.[213] Future animal work combining optogenetic stimulation with functional MRI to enhance circuit mapping[214] will probably inform functional connectivity work, including the development of biomarkers and therapeutic targets, in stroke.

There are several ways to judge by analogy when considering various data analysis methods. For instance, recent work examining post-stroke language comprehension stroke found converging evidence from analyses involving voxel-based lesion-symptom mapping, resting-state functional connectivity and grey matter fractional anisotropy showing that damage to certain networks related to specific language comprehension deficits.[215] In addition to different analysis approaches, defining or redefining regions of interest and neural networks through many freely available

templates and parcellation schemes may also foster the creation of an analogous experimental setting. For example, across seminal task-oriented functional MRI studies, M1, SMA, premotor and parietal regions retained relevancy in motor recovery regardless of their defined boundaries by investigators.[24,33,34,216] For functional connectivity studies, modifying the choice of regions of interest contained in a network and/or the connections both within and between networks provides an additional example of analogy. The expansion of a predefined motor network to include additional intra- and interhemispheric connections, for example, also provides a more complete (and probably realistic) account of how the motor system operates among other functional networks.[60,180,217]

Similar connectivity changes across diverse brain networks supports analogy. The study of functional behavioural deficits beyond the motor domain using a broad compendium of behavioural assessments and tasks is another strategy for establishing similar albeit distinguishing experimental settings. By examining multiple neural networks and behavioural domains spanning motor, visual and verbal memory, language and attention, Siegel *et al.*[60] identified patterns of network-specific damage that corresponded to domain-specific deficits and also post-stroke changes in homotopic functional connections, which ultimately corresponded to generalized behavioural impairment across numerous domains. Embracing a multidisciplinary approach in connectivity-based research by considering neural networks and behavioural deficits beyond the motor realm parallels the clinical environment where multiple medical disciplines and specialties converge in order to optimize patient outcomes. Last, in accordance with analogy, a recent review examining functional connectivity across a spectrum of clinical disorders and diseases concluded that functional connectivity networks exist in 'virtually all brains'.[218] The establishment of causality between functional connectivity and behavioural recovery in one disease setting is therefore likely to strengthen the causal argument of functional connectivity driving recovery in other disease settings including stroke.

Conclusion

Sir Austin Bradford Hill[11] delivered his address, 'The Environment and Disease: Association or Causation?' nearly 60 years ago, providing members of the Section on Occupational Medicine with nine viewpoints to consider when examining potential causality between environmental hazards and disease. His intention was for individuals to use his viewpoints as a guide when questioning the cause-and-effect hypothesis. Since the inception of his tenets, scientific inquiry has evolved. The advent of major scientific discovery and innovation, including neuroimaging, have resulted in profound changes in the formulation and testing of experimental hypotheses. His message, however, remains relevant today with many adopting his viewpoints in their specific fields of study. The purpose of this review was to not only frame Bradford Hill's tenets in the context of functional connectivity and stroke recovery (Table 1), but to also impart the following messages and recommendations moving forward in an effort to shift the experimental paradigm from correlation to causation.

Data integration is an ongoing process

Hill[11] acknowledged that, 'All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge'.

This review serves as a starting point for the ongoing integration of the connectivity literature in stroke rehabilitation as it pertains to behavioural outcomes. The expectation is that advancements in neuroimaging and connectivity analyses in stroke will generate novel research questions and paradigms that will both enrich and challenge our current thinking and understanding. The examination of time-varying dynamic functional connectivity network states in stroke[118] and the removal of lesion-driven variance in resting-state functional MRI data through independent components analysis[219] are pertinent examples.

Many disciplines comprise the stroke rehabilitation field. Data integration across these disciplines ensures a more comprehensive understanding of stroke rehabilitation[12] and the role of functional connectivity in this field. Several of Hill's tenets, including plausibility and coherence, necessitate the incorporation of data across disciplines. A strong likelihood exists that functional connectivity measures are more informative in certain cohorts or at particular time points given the enormous heterogeneity present when studying stroke, its clinical phenotypes and rehabilitation outcomes. The integration of positive and negative findings is therefore indispensable to understanding and establishing causality. Earlier, we acknowledged a limited number of studies reported negative findings, which probably underscores a publication bias. While negative findings typically refute previously held beliefs and principles, they are critical assets in data integration. Negative findings stimulate innovation and judicious use of resources, methodology and subjects. It is our hope that researchers and publishers alike recognize this value moving forwards.

Validation studies are essential

In accordance with Hill's consistency tenet, the need for validation studies in stroke recovery remains strong and is important to understanding causality. Increasing concern for rigour and reproducibility spurred widespread availability of open-source datasets and code. The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Stroke Recovery working group and their big data (>2100 stroke MRIs) approach towards understanding brain–behaviour relationships[220] underscores the shift in research practices supporting data sharing. Validation is an important component in predictive modelling, a prevalent theme in stroke rehabilitation literature. As previously mentioned, future connectivity investigations should incorporate internal validation procedures, including cross-validation and bootstrapping strategies, to reinforce reproducibility.[221]

Recognizing why causality matters in stroke rehabilitation

'While it is scientifically satisfying to elucidate the many component causes of an illness, in public health, the more important emphasis is on the discovery of necessary or sufficient causes that are amenable to intervention.'[222]

If the intended goal of functional connectivity research in stroke rehabilitation is to advance rehabilitation practice through the development of prognostic biomarkers, novel treatment targets and individualized therapies, then consideration of these tenets in stroke research is vital. Computer scientist and philosopher, Judea Pearl,[223] developed a 'ladder of causation' with each rung representing a research question of increasing difficulty based on the intricacy of data required: (i) prediction; (ii) intervention; and (iii) counterfactuals. Many of the questions involving functional

connectivity in stroke rehabilitation reside on the lower rung of Pearl's ladder. We hope that implementation of Hill's causality tenets in future research pursuits will strengthen the quality of evidence required for prediction and enable the rehabilitation field to ascend Pearl's causation ladder, where other medical fields pursuing more intervention-based research questions currently reside. For instance, Siddiqi and colleagues[224] defined two neural circuits associated with distinct symptomology features of depression. These symptom-specific circuits were reproducible and predicted improvement in an independent sample and, thus, could serve as personalized neuromodulatory targets for the treatment of depression.

Functional connectivity research in stroke is moving in a similar direction. As illustrated before, measures of connectivity may serve as both therapeutic targets and indicators of disease state, further justifying why functional neuroimaging-based biomarkers are a developmental priority in stroke research.[3] Implementation of Hill's causal tenets should motivate researchers to formulate and tackle crucial research questions to advance knowledge and clinical utility of connectivity research in stroke rehabilitation.

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Competing interests

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