Contribution of Neuro-Imaging for Prediction of Functional Recovery after Ischemic Stroke

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Keywords

Imaging · Stroke · Recovery · Computed tomography · Magnetic resonance imaging · Positron emission tomography · Diffusion tensor imaging

Abstract

Prediction measures of recovery and outcome after stroke perform with only modest levels of accuracy if based only on clinical data. Prediction scores can be improved by including morphologic imaging data, where size, location, and development of the ischemic lesion is best documented by magnetic resonance imaging. In addition to the primary lesion, the involvement of fiber tracts contributes to prognosis, and consequently the use of diffusion tensor imaging (DTI) to assess primary and secondary pathways improves the prediction of outcome and of therapeutic effects. The recovery of ischemic tissue and the progression of damage are dependent on the quality of blood supply. Therefore, the status of the supplying arteries and of the collateral flow is not only crucial for determining eligibility for acute interventions, but also has an impact on the potential to integrate areas surrounding the lesion that are not typically part of a functional network into the recovery process. The changes in these functional networks after a localized lesion are assessed by functional imaging methods, which additionally show altered pathways and activated secondary centers related to

residual functions and demonstrate changes in activation patterns within these networks with improved performance. These strategies in some instances record activation in secondary centers of a network, for example, also in homolog contralateral areas, which might be inhibitory to the recovery of primary centers. Such findings might have therapeutic consequences, for example, image-guided inhibitory stimulation of these areas. In the future, a combination of morphological imaging including DTI of fiber tracts and activation studies during specific tasks might yield the best information on residual function, reserve capacity, and prospects for recovery after ischemic stroke.

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Introduction

Stroke is a major global health problem and a leading cause of long-term adult disability worldwide. Despite a statistically significant reduction in the rates of incidence, mortality, and disability-adjusted life years from 1990 to 2013, the absolute number of people affected by stroke has increased significantly [1]. Only a small proportion of stroke survivors (approximately 14%) achieve full recovery of activities of daily living, while 25–50% require some assistance, and approximately half experience long-term dependency [2]. As a consequence, the absolute number

of disability-adjusted life years due to ischemic stroke (more than 47 millions) is dramatically high. Additionally, stroke should no longer be regarded as a disease of the elderly, as two-thirds of all stroke occur among persons of age below 70 years.

With stroke, the life of an individual undergoes a complete change – and the quality of life is significantly affected by decisions made in the initial period. One decision – which has to be made without delay due to the progress of brain damage with the duration of ischemia [3] – is on the acute treatment, and must be based on an estimation of efficacy of therapeutic strategies available and possible in a single case. According to common guidelines, patients with an acute cerebrovascular attack should be admitted to a specialized and adequately equipped hospital or stroke unit, where the decision on the best treatment will not only be based on clinical data [4], but also be supported by results from imaging and laboratory tests. At least one imaging study – computed tomography (CT) or magnetic resonance imaging (MRI) – is required to prove the diagnosis and rule out large morphological lesions, but simple and even complex clinical scores including morphologic imaging data require perspective studies to prove their validity for the prediction of therapeutic efficacy [5]. Since the existence of functionally impaired but morphological intact tissue is the prerequisite for the efficacy of reperfusion therapy in acute ischemia, many studies testing invasive treatment in the first hours after stroke were based on penumbral/mismatch imaging for recruiting patients [6–9]; however, criteria for the prediction of efficacy in individual cases were not assessed.

The aim of this review is not to describe whether the data collected from acute stroke patients are useful for the selection of an individualized treatment, but to collect evidence to establish that neuroimaging data may be helpful for the prediction of recovery and long-term outcome. This prediction should be achieved in the subacute stage 1–3 weeks after the attack and is important for informing patients and their relatives properly on realistic and attainable goals for treatment and rehabilitation, for planning of discharge, and for anticipating possible consequences for home adjustments and community support [10]. Table 1 summarizes the approaches for the prediction of outcome after ischemic stroke with stepwise increasing complexity of clinical data and addition of various imaging results.

Several systemic reviews have discussed the relationship of standardized measures to various aspects of stroke outcome and recovery, including quantification of neu-

rologic deficits, functional outcome, and quality of life [11, 12]. A systemic review of prognostic studies [12] indicated that age and motor weakness were important predictive variables of outcome, in addition to stroke severity; however, gender and presence of vascular risk factors were not. Employing simple models, a modestly large percentage of patients could be correctly classified with respect to survival and functional recovery (70.4–72.9% [13]), and with respect to the severity of impairment on BI (severe vs. mild neurologic deficits, AUC 0.789–0.808 depending on the time of assessment 2–5 days, [14]). The addition of more clinical variables in a relatively simple model improved the prediction accuracy slightly (83.9% [15]). The complex model based on an integer score from age, severity of stroke at admission by National Institute of Health Stroke Scale (NIHSS), time from stroke onset to admission, range of visual fields, acute glucose value, and level of consciousness reached an AUC of 0.850 in the original population and of 0.903 in a stroke population pooled from 3 centers [16] and was superior to the prediction by experienced physicians (3 months mRS: 286.5 vs. 56.8% [17]). The changes on the NIHSS and of symptoms and signs of traditional Chinese medicine during the first 5 days after stroke predicted the 90-day outcome [18]. As motor functions and walking are in the center of rehabilitative activities, several studies concentrated on the prediction of recovery of these modalities and developed special models for this application [19–21]. Chances for improvement of post-stroke aphasia can be estimated from the performance in word repetition from a language screening task, supporting the importance of perception and motor production for recovery of language function [22]. Additionally, studies of evoked potentials are helpful to assess the potential for functional recovery and to select patients who can benefit from targeted rehabilitative procedures [23]. Recently it was also shown that the causative classification of stroke is valid for the prediction of recovery [24].

Neuroimaging is now widely available and forms a routine in the clinical work-up of stroke patients. Imaging studies provide valuable insights into the pathophysiology of stroke and the extent of injury, and have the potential to improve the accuracy of stroke outcome prediction (Table 1). However, more studies are needed to establish conclusively which biomarkers are best predictors of functional recovery after stroke [25]. Current evidence suggests that the addition of neuroimaging data to models containing clinical predictors yields clinically important increases in predictive accuracy [21]. In this review, which is an update of a previous publication [26],

Table 1. Attempts for the prediction of outcome after ischemic stroke: application of increasingly complex clinical data and addition of results from imaging studies

Clinical data	
Individual variables	Age, initial neurological status, arm paresis, ability to walk, prestroke independence, previous stroke (Veerbeek et al. [12], 2011)
Scores	National Institute of Health Stroke Score (NIHSS) (Weimar et al. [120], 2004, Kwakkel et al. [14], 2010)
Indices	Age and NIHSS (König et al. [13], 2008) Barthel Index (Granger et al. [121], 1979) Functional Independence Measure (Alexander et al. [122], 1994)
Models	– Including age, upper limb paralysis, NIHSS, urinary catheter, oxygen administration (Muscari et al. [15], 2011) – Including age, prestroke independence, arm paresis, ability to walk, stroke severity score (Reid et al. [123], 2010) – Including age, sex, prestroke disability, dysarthria, urinary incontinence, limb deficit (Tilling et al. [124], 2001)
Complex model: ASTRAL	Age, NIHSS, time from symptom onset to admission, stroke-related visual field deficit, acute blood glucose value, level of consciousness (Ntaios et al. [16], 2012)
Addition of imaging modalities*	Volume of infarct on CT or MRI, hemorrhagic transformation or intracerebral hemorrhage on CT or MRI, location and size of infarct: ASPECTS Dense middle cerebral artery sign on CT Volume of early irreversible damage: DWI Affected fiber tracts: DTI
Addition of data on blood supply	Vessel occlusion on angiography, CT- or MR-angiography Collateral flow on CTA or MRA Perfusion in tissue: pCT, PWI Mismatch/penumbra: PW/DWI
Addition of functional imaging	fMRI at rest and during activation by specific tasks PET at rest and during activation by specific tasks
* For references, see text.	

the contributions of various neuroimaging modalities for the prediction of recovery and of functional outcome in patients after ischemic stroke and their role in assessing the efficacy of rehabilitation therapies, both in clinical trials and in individual patients, are discussed.

Structural Imaging

Computed Tomography

The routinely used imaging procedure in acute stroke is CT, which allows differentiation between hemorrhagic and ischemic stroke, localization, and extent of the lesion, and assists in decision-making regarding the administra-

tion of potentially risky stroke therapies including thrombolysis and endovascular thrombectomy. Initial infarct volume determined within 72 h of ischemic stroke onset was an independent predictor of outcome at 90 days, along with age and NIHSS score [27]. The prognosis for stroke recovery is also related to the site of ischemic brain injury: Strokes in the insular region has been associated with increased mortality [28]. In a prospective study of patients with acute ischemic stroke, anterior choroidal infarcts were found to have an intermediate long-term prognosis between lacunar infarcts and large artery territory hemispheric infarcts [29]. Lesions located in the internal capsule demonstrated a worse prognosis for recovery of hand motor function at one year than strokes in the corona radiata

or motor cortex [30]. Evidence of brain edema predicts poor outcome after non-lacunar ischemic stroke [31].

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was developed to evaluate the extent and location of ischemic changes in 10 regions within the territory of the middle cerebral artery (MCA) [32]; this scale is related to functional outcome on mRS at 3 months post-stroke. In combination with age and severity of neurologic deficits, a subacute ASPECTS of more than 5 had a significant predictive value of greater functional independence at 3 months ($R^2 = 0.701$) and 1 year post-stroke ($R^2 = 0.528$) [33]. Also, the initial lesion volume was a strong and independent predictor of stroke outcome in a statistical regression model that also accounts for age and NIHSS [27]. As a consequence, the inclusion of lesion size in predictive models of outcome has the potential to improve stratification of samples and increase the power for effective detection in trials of acute therapies and of rehabilitative strategies in ischemic stroke. The evaluation of stroke volume and localization when combined with NIHSS showed potential predictive value, which might be further improved by several biomarkers, namely the S100 calcium-binding protein B, C-reactive protein, matrix metalloproteinases, and cerebral natriuretic peptide [34].

The predictive value of complex clinical models, such as ASTRAL [16], can be improved by the addition of dense MCA sign from CT [35]). This score could predict the outcome after thrombolysis with high accuracy (AVC 0.84), and was better than the prediction by experienced physicians (mRS5–6 at 3 months: 80.4 vs. 40.4% [17]).

Magnetic Resonance Imaging

High resolution structural MRI sequences identify even small stroke lesions, but relating the size of lesions to clinical impairment and functional outcome is difficult, especially since small lesions of the subcortical white matter or the brainstem can produce disproportionate clinical disturbances [36]. Therefore, lesion location also needs to be considered. Involvement of the corticospinal tract by the ischemic lesion is a particularly important factor, limiting the upper limb motor recovery [37], while the impact on gait is less pronounced [38]. Severe white matter disease may also be an independent predictor of poor functional outcome [39].

Hemorrhagic transformation (HT), visualized on non-contrast CT or T2*-weighted MRI sequences is a biomarker of potentially poor outcome. Gradient Echo Sequences MRI is significantly more sensitive to HT than CT or other MRI sequences [40]. Rating scales incorpo-

rating the extent of hemorrhage along with measures of neurologic deterioration have shown that the presence of HT, particularly when considered “symptomatic ICH”, is predictive of poor functional outcome. However, compared to other predictive factors, the contribution of symptomatic ICH may be smaller [41]. Of interest, even “asymptomatic HT” appears to be a predictor of poor outcome [42].

Diffusion-weighted imaging (DWI) provides an early, distinct, and sensitive measure of both the size and location of ischemic brain lesions. In patients with non-lacunar strokes in the anterior circulation, lesion volume assessed by DWI in addition to age and NIHSS score was an independent predictor of outcome, separating patients with a final BI above or below 85 [43]. DWI lesion volume significantly increased the power of some, but not all [44] prediction models; however, this effect was not large enough to be clinically significant in other analysis [45]. The likelihood of achieving excellent neurological outcome diminished substantially with the growth in DWI infarct volume in the first 5 days after ischemic stroke of mild-to-moderate severity [46]. Some studies have incorporated information on infarct location to predict neurologic deficits [47, 48].

Diffusion tensor imaging (DTI) permits visualization of white matter pathways in the brain and has been specifically used to demonstrate damage to the corticospinal tract, which is commonly associated with motor impairment in chronic stroke patients [49]. DTI measures may also be used to predict long-term outcome (30). The initial fiber number ratio calculated for the affected corticospinal tract normalized to the contralateral unaffected side predicted motor outcome after 1 year; in a multivariate analysis, the initial fiber number ratio was an independent predictor of motor outcome ($p = 0.031$), improving the prediction compared with using only initial Fugl-Meyer score, age, and stroke volume ($p = 0.026$) [50]. DTI lesions visible within 3 weeks after stroke were associated with motor deficits at 3 months in supratentorial stroke patients with severe motor involvement [51]. In one study, the extent of damage to the corticospinal tract following a corona radiata infarct assessed 7–30 days after a stroke was related to the motor function of the affected hand 6 months later [52, 53]. The damage to the pyramidal tract assessed by fractional anisotropy (FA) in DTI progressively decreased in the medulla as well as in proximal portions 1–12 weeks after pontine infarction, and these antero-grade and retrograde degenerations were accompanied by deterioration in the clinical scales of motor function [54]. The prediction of motor impairment and recovery was

improved; not only the pyramidal tract, but also the alternative motor fibers were included in the classification of damage [37]. Damage to the posterior limb of the internal capsule within 12 h of symptom onset correlated well with motor impairment at 30–90 days; the sensitivity and specificity of the DTI parameters were superior to lesion volume in the corona radiata or the cortex and to baseline clinical scores [55]. A random effects model developed on the results from 11 selected studies revealed that the DTI parameter FA is a significant predictor of upper limb motor recovery after ischemic stroke [56].

Efficiency of rehabilitative therapy has been related to DTI parameters of individual tracts and tract combinations, and may indicate a patient's individual recovery potential and the optimal rehabilitative intervention [57]. Additionally, gains from treatment were related to the degree of injury to specific motor tracts (descending from primary motor cortex, supplementary motor area, dorsal premotor cortex, and ventral premotor cortex, respectively), and the damage to these tracts had a greater impact on the therapeutic effect than the infarct volume or baseline clinical status [58].

The effect of brain computer interface technology in rehabilitation strategies on upper-limb motor activities could be related to DTI measures of the posterior limb of the internal capsule (FA, axial, radial, and mean diffusivity): lower diffusivity and higher FA values measured immediately and 1 month after interventions were significantly correlated to motor outcomes [59].

Non-motor pathways can also be studied by relating their damage to higher brain function, for example, language performance. Lower FA values in the superior longitudinal and arcuate fasciculi of the left hemisphere were correlated with decreased ability to repeat spoken language, and lower FA values in the arcuate fasciculus were associated with comprehension deficits; these relationships were independent of the degree of damage to cortical areas [60]. The outcome of aphasia was improved in patients whose left FA could be reconstructed [61].

All these data stress that the connectivity in networks, as assessed by DTI, is likely to be more important for outcome and recovery than the extent of the primary structural lesion. However, despite all these promising results, structural neuroimaging neither provides information on the cause of the ischemic lesion and compensatory mechanisms, nor indicates whether or how surviving tissues are working [62]. The individual markers for structural integrity – CT, MRI, and DTI – are not sufficient to reliably predict post-stroke recovery. Their validity might be improved by adding functional biomarkers, for example,

functional MRI and transcranial magnetic stimulation, in a combination of biomarkers [25]. The functional connectivity between cortical and subcortical components of neural networks determines the capacity for reorganization and recovery. The studies of these measures require modalities for physiologic, molecular, and functional imaging.

Assessment of Brain Blood Supply and Cerebral Perfusion

The reduction of regional cerebral blood flow below a critical threshold for a critical period of time causes ischemic tissue damage. This critical situation is usually triggered by the occlusion of the feeding vessel and the insufficiency of collateral perfusion. Occlusion of a large intracranial vessel, such as the basilar, internal carotid, or MCA, is associated with higher mortality and more severe permanent deficits, and therefore contributes predictive value to models of stroke outcome [63, 64]. Basilar and internal carotid artery occlusions detected by conventional angiography has the highest NIHSS scores [65] and the worst outcome [66], whereas normal angiograms predicted a good prognosis. Large vessel occlusion detected by CT angiography (CTA) in the first 24 h after the attack significantly increased the 6-month mortality (4.5-fold increase), and was negatively correlated to good outcome (mRS $\leq$ two-threefold reduction) [67]. Basilar and internal carotid occlusions independently affected the outcome in addition to age and NIHSS. Information from CT angiography contributed significantly to outcome prediction than the ASPECTS score [68, 69]. Stroke outcome prediction was improved when CTA results were combined with the NIHSS (STOP Stroke study [68]).

The final size of an infarct is not only influenced by the occluded vessel, but also by the extent and quality of collateral circulation to the affected brain area. Conventional angiography can demonstrate robust collateral flow, which has been linked to reduced infarct volumes; in cases receiving thrombolysis, collateralization was a significant univariate predictor in addition to occlusion type and recanalization [70, 71]. Rapid recruitment of sufficient leptomeningeal collaterals, as assessed by CTA, was related to favorable outcome, whereas patients with diminished sylvian and leptomeningeal collaterals had a greater risk of worsening [72]. Univariate analysis identified the grade of leptomeningeal vascularity as an independent predictor of good outcome [73]. Early CTP ASPECTS leptomeningeal collaterals in the M5 (parietal) region were independently associated with good functional outcome; when M5 collaterals score was added to

the NIHSS, a better prediction value was achieved (area under the curve: 0.752, $p < 0.001$) [74].

For perfusion parameters obtained by CT or MRI, a weak relationship of PWI lesion size early after the ictus [75] as well as perfusion CT-mismatch [76] and mRS score 3 months after the stroke was obtained, confirming early results of the relationship between cerebral blood flow measured with 133 xenon [77] or with 99 m Technetium-labeled hexamethyl propylene amine [78] and final outcome. Several studies have suggested that ASPECTS applied to CTP is more accurate in predicting outcome compared to NCCT ASPECTS [79, 80]. Location-weighted CTP analysis may be a valuable tool for predicting motor improvement and language improvement [81, 82]. For multimodal MRI, addition of both DWI and MTT lesion volumes to NIHSS information is superior to NIHSS alone in predicting outcomes [83, 84]. In one study, it was found that the cerebral blood volume defined by CTP ASPECTS was the best predictor of clinical outcome in acute ischemic stroke as it recognizes the infarct; it was better than CTP mismatch implying that the extent of the core is the main determinant of outcome, irrespective of the penumbra site [85]. CBV-ASPECTS was also a significant predictor of clinical outcome in patients with acute ischemic stroke treated with mechanical thrombectomy [86].

Penumbra imaging and its role in selecting patients for reperfusion therapies is discussed in a recent review [87]. However, a number of prediction scores have been developed and applied in cohorts undergoing reperfusion therapies. The effect of therapy with rtPA was related to clinical data and findings in imaging [88], and a special combined score (DRAGON) could predict poor and good outcome (AUC 0.82–0.84 respectively) [89, 90]. A 5-item scale including infarct volume was able to predict the outcome after iv-tPA treatment in the DEFUSE cohort with 83% sensitivity and 86% specificity [91]. Reperfusion demonstrated on perfusion weighted-MRI was associated with good clinical outcome [92–95]. Even late reperfusion seen in PWI after embolectomy predicted improved outcome [6]. A score combining age, glucose, NIHSS, and ASPECTS of ≥ 5 predicted poor outcome after intra-arterial therapy [96].

Role of Functional Imaging in Stroke Patients

The functional deficit after a focal brain lesion is determined by the localization and the extent of tissue damage; recovery depends on the adaptive plasticity of the undamaged brain, especially the cerebral cortex, and of the non-affected elements of the functional network. Since destroyed tissue usually cannot be replaced in the adult hu-

man brain, improvement, or recovery of neurological deficits can be achieved only by the reactivation of functionally disturbed but morphologically preserved areas or by recruitment of alternative pathways within the functional network. This activation of alternative pathways may be accompanied by the development of different strategies to deal with the new functional-anatomical situation at the behavioral level. Additionally, the sprouting of fibers from surviving neurons and the formation of new synapses could play a role in long-term recovery. These compensatory mechanisms are expressed in altered patterns of blood flow or metabolism at rest and during activation within the functional network involved in a special task, and therefore functional imaging tools can be applied successfully for studying physiological correlates of plasticity and recovery noninvasively after localized brain damage. The observed patterns depend on the site, extent, and also on the type and dynamics of the development of the lesion; they change over time and hence are related to the course and recovery of a deficit. The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities, such as positron emission tomography and functional MRI (fMRI).

For the analysis of the relationship between disturbed function and altered brain activity, studies can be designed in several ways: measurement at rest, comparing location and extent to deficit and outcome (eventually with follow-up); measurement during activation tasks, comparing changes in activation patterns to functional performance; and measurement at rest and during activation tasks early and later in the course of disease (e.g., after stroke) to demonstrate recruiting and compensatory mechanisms in the functional network responsible for complete or partial recovery of disturbed functions. Only a few studies have been performed by applying this last and most complete design together with extensive testing for the evaluation of the quality of performance finally achieved. A large amount of data has been collected over the past years with functional imaging of changes in activation patterns related to the recovery of disturbed function after stroke [97–103].

Motor and Somatosensory Deficits

The degree of motor impairment and the potential for motor recovery depends on the site and extent of the lesion, the combination of lesions in cortical areas and fiber tracts, and the involvement of deep gray structures, for example, the basal ganglia, thalamus, and brainstem. Mo-

tor recovery is not rapid during the first month after stroke and reaches a plateau within 3 months; activities of daily living do not improve beyond 6 months poststroke [104]. The motor recovery plateau can be predicted for individual patients by combining clinical measures with an objective evaluation of descending motor pathway integrity [105]: assessment of shoulder abduction and finger extension is combined with transcranial magnetic stimulation to test the functional integrity of the corticomotor pathway and MRI to detect the extent of damage to the posterior limb of the internal capsule. The used algorithm predicted individual patient's potential to make complete, notable or limited recovery, or no recovery of upper limb functions within 3 months, measured with the Action Research Arm Test [104].

A clear concept of "neuronal plasticity" for motor recovery is still missing: one recent review concluded that "motor recovery after stroke depends on a variety of mechanisms including perilesional motor reorganization, use of motor pathways in subcortical structures, use of collateral pathways in the ipsilateral hemisphere, use of collateral pathways in the contralateral hemisphere, or possibly the development of entirely new motor networks" [99]. A combination of structural and functional imaging methods improves monitoring and predicting hand-motor outcome after stroke: lesions are mapped by T1-weighted imaging; DWI with DTI measures structural connectivity as well as intactness of corticospinal tract, resting stroke fMRI assesses functional connectivity between the different regions of a network; activation fMRI demonstrates regions involved in a function even when alternative pathways are used due to a damage in the primary centers [106], this combination of biomarkers permits the classification of patients into different subgroups with respect to probable outcome, and may help in selecting specific strategies for rehabilitation.

As a consequence, most fMRI or positron emission tomography studies reported a widespread network activated in both hemispheres with active or passive movements. Changes in the damaged and the undamaged hemispheres are observed, but ipsilateral activation of motor cortex is consistently stronger for the movement of paretic fingers after the recovery from stroke. Movements of the unaffected hand induce activation of the contralateral cerebral cortex as in normal subjects. Additionally, the extent of activation in motor cortex is enlarged, and usually extends to the premotor and insular cortex. This stresses the importance of ipsilateral cortical recruitment in motor recovery; one study demonstrated a direct relationship between activation in the ipsilesion-

al motor cortex, supplementary motor cortex and insula, and recovery 1 year after stroke [107]. Task-oriented arm training increased the activation bilaterally in the inferior parietal area, in premotor areas, and in the contralateral sensorimotor cortex, as a substrate of bilateral functional brain reorganization [108]. Newly learned movements involve larger cortical territories, and this effect is dependent on the intensity of rehabilitative training. Another important finding suggests that homotopic areas in the unaffected hemisphere actually inhibit voluntary movement of the paretic hand [109], and thereby impair recovery of function. Recovery of function after stroke also leads to substantial changes in the activity of the proprioceptive systems, reflecting an interhemispheric shift to stimuli associated with recovery [110].

Post-Stroke Aphasia

Studies of glucose metabolism in aphasia after stroke have shown metabolic disturbances in the ipsilateral hemisphere caused by the lesion and in the contralateral hemisphere caused by functional deactivation (diaschisis; review in [111]). In right-handed individuals with language dominance in the left hemisphere, the left temporo-parietal region, in particular the angular gyrus, supramarginal gyrus, and lateral and transverse superior temporal gyrus (STG) are most frequently and consistently impaired, and the degree of impairment is related to the severity of aphasia. The functional disturbance, as measured by rCMRGlc in speech-relevant brain regions early after stroke, is predictive of the eventual outcome of aphasia. Also, the metabolism in the hemisphere outside the infarct was significantly related to the outcome of post-stroke aphasia, a finding supporting previous results of a significant correlation of CMRGlu outside the infarct with functional recovery [112].

Additionally, the functionality of the bihemispheric network has a significant impact on the outcome; although the brain recruits right-hemispheric regions for speech-processing when the left-hemispheric centers are impaired, outcome studies reveal that this strategy is significantly less effective than repair of the speech-relevant network in adults [113]. That the quality of recovery is mainly dependent on undamaged portions of the language network in the left hemisphere and to a lesser extent on homologous right hemisphere areas can be deduced from activation studies in the course after post-stroke aphasia [114]. The differences in improvement of speech deficits were reflected in different patterns of activation in the course after stroke: the subcortical and frontal groups improved substantially and activated the

right inferior frontal gyrus and the right STG at baseline and regained regional left STG activation at follow-up. The temporal group improved only in word comprehension; it activated the left Broca area and supplementary motor areas at baseline and the precentral gyrus bilaterally as well as the right STG at follow-up, but could not reactivate the left STG. These results were confirmed in comparable studies [115–117].

The activation studies in the course of recovery of post-stroke aphasia suggest a hierarchy of various mechanisms for the compensation of the lesion within the functional network:

- Optimal recovery can only be achieved by restoration of the original activation pattern after small brain lesions outside primary centers.
- If primary functional centers are damaged, reduction of collateral inhibition leads to the activation of areas around the lesion (intrahemispheric compensation).
- If the ipsilateral network is severely damaged, reduction of transcallosal inhibition causes the activation of contralateral homotopic areas, which is usually not as efficient as intrahemispheric compensation. In most instances, the disinhibition of homotopic areas contralateral to the lesion impairs the capacity for recovery [118].

Neglect

Spatial neglect can either spontaneously resolve or persist after stroke – and persisting neglect is associated with poor recovery. A longitudinal fMRI study revealed different signatures: a favorable course of recovery was specifically associated with increased activation in essen-

tial functional nodes, when the left prefrontal region replaces the irreversibly damaged ventral attention system and supports spatial performance, driving the preserved ipsilesional dorsal attention system. The strength of functional connectivity between right parietal and left prefrontal region might predict the course of recovery [119].

Conclusions

Prediction of long-term functional outcomes following ischemic stroke is complex; imaging approaches in both the hyperacute and subacute stages provide added value over clinical prediction variables. In the future, this information, combined with clinical data may be used to guide both acute and rehabilitative therapies, and provide valuable prognostic information. Large databases including both clinical and imaging data may be developed to allow prognostic and therapeutic decision-making to be individualized based on specific clinical factors and individual pathophysiology.

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