

## FUNCTIONAL IMAGING IN THE ASSESSMENT OF CAPABILITY FOR RECOVERY AFTER STROKE

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**After an ischaemic lesion preserved components of a functional network are utilized for recovery from neurological defects. The hierarchy of the individual parts within the damaged network, however, determines the quality of the outcome. This could be clearly demonstrated for the complex network of language ability, for which the left temporal region plays an integrative role: only if the left temporal regions are morphologically preserved and can be reactivated in imaging studies of speech performance was the outcome of poststroke aphasia satisfying. In brain functions with a less pronounced hemispheric specialization the effect of disturbed centres in the dominant hemisphere might be less accentuated. Functional neuroimaging studies might help to estimate prognoses of functional outcome in early states after stroke and to evaluate the efficiency of strategies of rehabilitative measures and of adjuvant drug therapy.**

*Key words:* aphasia, motor deficit, functional imaging, positron emission tomography, functional MRI

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### INTRODUCTION

Clinical recovery of neurologic function after human stroke is seen frequently and has been described in many publications (1–5). In particular, language and motor functions often recover close to completely from initial impairments of mild to moderate severity; yet, the physiologic correlates of that recovery are less clear. Most likely, oedema and its resolution play a role, but there is little information regarding oedema's influence on neuronal function (6). Functional recruitment of additional neurons through appropriate training has been demonstrated, mainly by means of invasive electrophysiologic methods, in experimental animals (7, 8) and is also likely to occur in humans. However, direct evidence is difficult to ascertain. There may also be rearrangements of large-scale neural networks involving ipsilateral or contralateral cortical areas, as suggested by electrophysiologic evidence.

The motor network is reorganized with involvement of descending motor pathways contralateral to the lesion in patients after hemispherectomy and severe hemispheric lesions (9). This may be because of the unmasking of existing but functionally inactive pathways, the sprouting of fibres from surviving neurons and formation of new synapses, neuronal group selection, or the redundancy of central nervous system circuitry allowing alternative pathways to take over functions (10–12). Functional imaging techniques provide a means of studying physiologic correlates of plasticity and recovery noninvasively in stroke patients. Early techniques, such as cerebral blood flow (CBF) measurements by single or multiple detectors or planar imaging devices, demonstrated remote functional effects of focal ischaemic lesions on resting CBF. Tomographic CBF techniques, such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), demonstrated these effects with improved specificity and spatial resolution.

In recent years, functional changes during the execution of neuronal function have been elucidated by demonstration of an increase in CBF or cerebral metabolic rate of glucose (CMRGlc) in activated brain structures. Most recently, functional magnetic resonance imaging (fMRI) became available for such activation studies, providing further increases in spatial and temporal resolution (13). These studies primarily address representational plasticity, i.e., changes in the topographic representation of specific neural functions in brain. In principle, aspects of molecular and cellular plasticity (11, 14) could also be studied *in vivo* by use of specific radiotracers to assess changes of neurotransmitter synthesis and receptor binding capacity (15). Degeneration of white matter tracts that accompany neuronal reorganization can be studied with magnetic resonance imaging (MRI; (16)) and magnetic resonance spectroscopy (MRS) (17).

A large amount of data has been collected over the past years with functional imaging of changes in activation patterns related to recovery of disturbed function after stroke (18–21). In this short review we summarize our own findings from PET activation studies in the recovery of patients suffering from aphasia or motor deficits.

### DESIGN AND RATIONALE OF FUNCTIONAL IMAGING STUDIES

The role of areas in the left and right hemisphere in recovery and the reorganization of the intra- and interhemispheric network af-

ter ischaemic or other localized lesions can be studied by functional imaging methods. Several designs can be applied to such studies: measurement at rest, comparing location or follow-up (or both) to deficit and outcome; measurements during activation tasks, comparing changes in activation patterns to functional performance; and measurements at rest and during activation tasks early and later in the course of disease (after stroke) to demonstrate recruiting and compensatory mechanisms in the functional network responsible for complete or partial recovery of disturbed function. Only a few studies have been performed applying this last and most complete design together with extensive testing for the evaluation of the quality of finally achieved performance.

## POSTSTROKE APHASIA

Aphasia is a severely incapacitating symptom of stroke and is a main cause of functional disturbance. Estimates suggest that more than 20% of patients suffering a stroke develop aphasia, while 10–18% of survivors are left with a persistent speech deficit (22). Most patients with aphasia due to acute non-progressive brain damage, such as in the case of stroke or head injury, show some degree of recovery of language function during the days, months, or even years following the initial insult. Recuperation is variable, ranging from barely noticeable improvement of auditory comprehension of the global aphasia to the apparently complete recovery of the patient with mild fluent aphasia due to a small subcortical stroke. It is also well known that improvement can be observed not only in patients submitted to language rehabilitation, but also in cases who have not undergone any specific treatment.

Studies of glucose metabolism after stroke have shown that the left temporo-parietal cortex is crucial for language perception (23, 24) and that the metabolic disturbance in these areas is related to outcome (25). Investigations in the subacute state after stroke showed a highly significant correlation with language performance assessed at follow-up after two years (26). The receptive language disorder correlated with  $rCMR_{glc}$  in the left temporal cortex and word fluency correlated with  $rCMR_{glc}$  in the left prefrontal cortex. These results indicate that the functional disturbance as measured by  $rCMR_{glc}$  in speech-relevant brain regions early after stroke is predictive of the eventual outcome of aphasia. However, not only functional deactivation (diaschisis) (27) but neuronal loss may also contribute to metabolic and perfusional changes in the neighbourhood of the infarct, and the condition of the surrounding tissue may affect the recovery of individual patients. On this

basis it is not surprising that, in patients with a poor outcome of poststroke aphasia, metabolism in the hemisphere outside the infarct was significantly less than in those with good language recovery, indicating significant cell loss caused by the ischaemic episode outside the ischaemic core (25). In addition, the functionality of the network was reduced in patients with an eventual poor outcome; during task performance, patients with an eventual good recovery predominantly activated structures in the ipsilateral hemisphere.

One of the central issues of aphasia research is the question of why recovery from aphasia takes place and what the responsible mechanisms for this recovery are. Converging evidence from clinical studies and neural imaging studies of aphasic patients suggests that primary candidates for recovery in right-handed, left-hemisphere language dominant patients include undamaged portions of the language network in the left hemisphere and, to a lesser extent, homologous right hemisphere areas. Functional imaging studies focused also on the influence of treatment on the course and extent or neural organization and on the possibility that certain treatments could enhance neural reorganization. In these studies of reorganisation of the functional network in the course of aphasia it is important to take into consideration the specificity of the tasks, the influence of site and extent of lesion and the effect of treatment focused on a particular language domain on recruitment of different aspects of the language network,

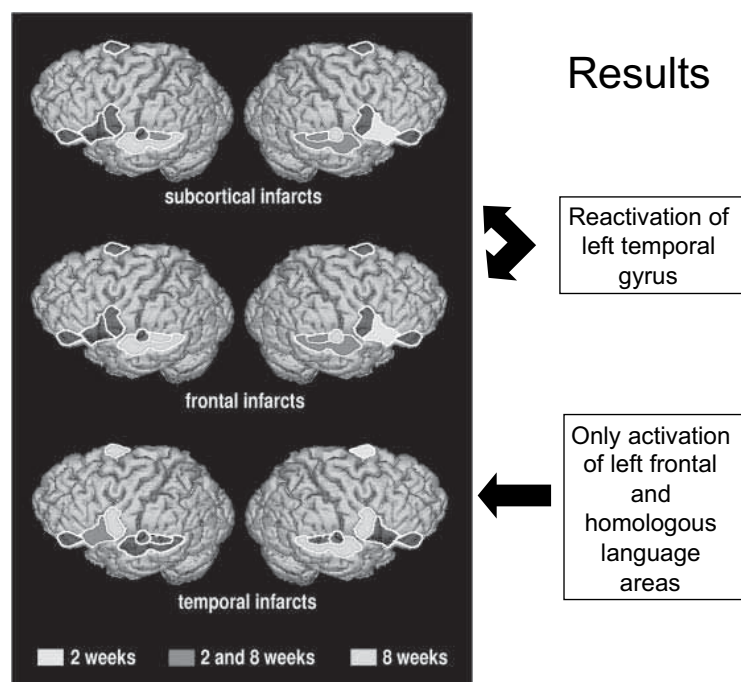


Fig. 1. Significantly activated volumes of interest in aphasic patients at initial (2 weeks) and follow-up (8 weeks) PET scans. Subcortical and frontal infarcts reactivate left temporal gyrus and experience better recovery of language function than patients with temporal infarcts, who only activate left frontal and right temporal areas.

especially if compensatory treatment to access-limited functional responses would only stimulate required pathways, but would do little to stimulate reorganisation of the language system (28).

Studies are needed that precisely measure changes in neural networks involved in language processing during the course of recovery. Further, specific changes in neural networks associated with different outcome and with certain behavioural changes induced by treatment need to be mapped in the brain.

We have followed up these questions in groups of patients with aphasia after stroke (29). The method used for functional imaging was PET, by which regional glucose metabolism or blood flow can be measured and a specific brain function can be localized by subtracting the image under resting condition from the image obtained during performance of the specific task. The basis for our further studies is the task of repeating words. Repeating words in 10 normal controls activates blood flow by more than 10% in both upper temporal gyri, by 5–10% in planum temporale and Heschl's gyrus, of both sides and in the lower part of the central gyrus of the left side, and by less than 5% in the left Broca area. This test procedure was applied to 23 patients with aphasia of different types. Morphological defects were defined on MRI/CT, and the patients were grouped according to the site of the lesion. Activation PET studies were performed in the subacute stage approximately 2 weeks after the stroke and repeated 6 weeks later. On matched MRIs regions of interest were defined in 14 identified structures of the bilateral language-related network.

The three groups of aphasic patients showed a different pattern for activation in the acute and chronic phase, and their improvement was different. Whereas subcortical and frontal infarcts improved considerably in several tests, temporal infarcts showed only little improvement. These differences in improvement of speech deficits were reflected in different patterns of activation in the course after stroke (Fig. 1). The subcortical and frontal groups improved substantially and activated the right inferior frontal gyrus and the right superior temporal gyrus (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 differential activation patterns were also obvious when subcortical and frontal infarcts were grouped together according to the extent of improvement: those with a decrease in Token test errors by more than 50% could activate the left superior temporal gyrus, while those with a more unfavourable and unsatisfactory outcome were not able to do this. Similar reactivation patterns were observed in smaller groups of patients (30, 31).

These differential activation patterns suggest a hierarchy within the language-related network regarding effectiveness for improvement of aphasia, i.e. right hemisphere areas contribute, if left hemispheric regions are destroyed. Efficient restoration of language is usually only achieved if left temporal areas are preserved and can be reintegrated into the functional network.

## EFFECT OF TREATMENT IN POSTSTROKE APHASIA

Whereas the effect of physiotherapy for improvement of sensorimotor deficits is unchallenged, the efficiency of speech therapy is still controversial with several randomised controlled trials yielding no difference in outcome between treated and untreated groups (32, 33). Many trials were undertaken to enhance the recovery from aphasia with adjuvant pharmacotherapy, but again, only a few studies demonstrated efficacy. In a recent double-blind placebo-controlled study Walker-Batson et al. (34) observed a significantly higher gain score in patients treated with dextroamphetamine before speech therapy sessions compared to the placebo group, but the difference was not significant at 6 months follow-up. A large Cochrane review (35) identified piracetam as the only drug with a significant effect on recovery of language, which was also observed in a large multicentre trial (36). In order to investigate if the effect of piracetam is reflected in altered activation patterns, we performed a study on 24 patients with aphasia after stroke. These patients, who were all receiving speech therapy, were randomly assigned to placebo or 2×2.4 g piracetam. Approximately two weeks after the stroke, clinical and neuropsychological tests as well as flow PET studies at rest and during activation were performed. Six weeks later the same procedure was repeated. Patients with ischaemic infarcts within the left MCA territory and a mild to moderate aphasia were included, while severe or repeated strokes or other severe diseases were excluded. The random assignment to treatment or placebo resulted in fairly comparable patient samples, with slightly larger infarcts in the placebo group. Language performance was tested by the Aachen Aphasia Test Battery; word fluency, memory and intelligence were also assessed. Brain imaging was performed with the same procedures as used in the previous study, with activation tested by word repetition, repeated four times for each condition in a balanced order. Again, regions of interest located within the language-related network were analysed.

With respect to performance in the aphasia tests, the piracetam group did significantly better especially in subtests reflecting the ability for spontaneous speech (Table I), whereas the placebo experienced – as the verum group did – improvements in Token test, reading and writing and comprehension. It was impressive to see that these differences in improvement were also reflected in differences in the achieved activation patterns (Table II): in the piracetam group, increase of activation was significantly higher in the left transverse temporal gyrus, the left triangular part of inferior frontal gyrus and the left posterior temporal gyrus after the treatment period, compared with the initial measures. The placebo group showed an increase in the activation effect only in the left vocalization area.

It might be concluded from the controlled clinical trials and our study of activation patterns that piracetam as an adjuvant to speech therapy improves recovery of various language functions, and that this effect is accompanied by task-related flow activation in eloquent areas of the left hemisphere. This again points to

the important role of (re)activated areas in the left hemisphere for recovery of the language function.

## APHASIA IN BRAIN TUMOURS

The speed in the development of a brain lesion may have an effect on the developing functional impairment and on the mechanism of compensation and reorganisation of the involved networks. In order to study the effect of a chronic, slowly evolving brain lesion on the language-related networks we investigated 61 patients with brain tumours in the dominant hemisphere, applying 0–15 water and PET for detecting cerebral blood flow changes under a verb generation task (37). In comparison to a healthy control group (n=12), in whom mainly left Brodman Area (BA) 44 and 45 (pars triangularis and opercularis of the inferior frontal gyrus), both superior temporal gyri and the left cerebellum were activated, in patients with left hemispheric tumours a significant flow increase was observed additionally in left BA 46 and 47 (G. frontalis medius and pars orbitalis of inferior frontal gyrus), in the anterior insula and the left cerebellum. Activations in the superior temporal gyrus were less marked and could also be seen outside the posterior upper temporal gyrus on both sides. Frontolateral activations in the non-dominant hemisphere were only observed in patients with frontal or temporal tumours. In 18 cases the laterality indices suggested reversed language dominance. Reversed speech dominance was related to the severity of the aphasia, and could be normalized with reactivation of left eloquent areas after successful tumour resection (Fig. 2).

## COMPENSATORY MECHANISMS IN APHASIA

The different patterns observed in poststroke and tumour-related aphasia could be interpreted as different compensatory mechanisms evolving during the development of the lesion. These compensatory mechanisms might be important for the chance of recovery. The specialization of different brain areas for definite functions and the lateralization of higher functions is, according to presently accepted hypotheses, a result of the inhibition of those parts of a network that are not participating in a special task (38). For this reason, neurons that are involved in a special task must inhibit neurons in neighbouring areas or in contralateral corresponding regions (39). Studies in brains of men and animals have indicated a reduction of neurons and of callosal fibres as a sequel of asymmetric lateralized function (40, 41), which could be caused by selective neuronal degeneration (apoptosis) adapting the neuronal population to the functional requirement of a brain region during development (42). These selected and specialized neurons additionally inhibit neurons in neighbouring brain regions that are not involved in the special task or in brain regions connected (even contralateral) to them by fibre-pathways (39, 43–45).

If the specialized neurons are damaged, the inhibition of

Table I. *Aachen Aphasia Test Battery: Significant improvement after treatment*

	Piracetam	Placebo
Spontaneous speech		
Communication	+ *	-
Articulation and prosody	-	-
Automatic speech	-	-
Semantic structure	+ ***	-
Phonological structure	-	-
Syntactic structure	+ *	-
Token Test	+ ***	+ ***
Repetition	-	-
Reading and writing	+ **	+ *
Confrontation naming	+ *	-
Comprehension	+ ***	+ ***

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001

neighbouring or collateral areas in the connection network breaks down, and the resulting disinhibition increases the areas activated by stimuli or tasks (7). Even contralateral corresponding regions are activated (46).

These mechanisms can be observed in the activation patterns after damage to the language network. The failure of inhibition in neighbouring regions results in intrahemispheric compensation which is usually related to better residual function, since homolateral original eloquent areas are involved.

With extensive damage and involvement of important areas of higher hierarchy (e.g. the left superior temporal gyrus) the inhibition via the corpus callosum breaks down and the disinhibition of transcallosal activity promotes interhemispheric compensatory mechanism; this mechanism permits some residual function which is, however, less effective than involvement of ipsilateral eloquent areas. This hierarchy in efficiency of compensatory mechanisms can be observed in the course of poststroke aphasia, where only the reactivation of ipsilateral eloquent areas results in satisfactory recovery of language function; it could also be demonstrated in a few cases of brain tumours, where reversed dominance was normalized after tumour resection, and language improved.

## MOTOR DEFICITS

Motor function may be impaired by damage to a widely distributed network, involving multiple cortical representations and complex fibre tracts. The degree of motor impairment and the potential for recovery depends on the site of the lesion, the association of lesions in cortical areas and in fibre tracts and the involvement of deep grey structures, e.g. the basal ganglia, thalamus and brain stem. The pattern of altered metabolism and blood flow and the patterns of activation after stimuli or during motor tasks are manifold and reflect the site and extent of the lesion, but they are also dependent on the paradigm of stimulus or task. With severe motor impairment, patients can not carry out complex or

even simple motor tasks, and the activation paradigm must be restricted to passive movement or imagination of motor performance. The diverging experimental conditions make the interpretation and comparison of different studies extremely difficult, and might help explain the lack of a clear concept of 'neuronal plasticity' applicable to recovery from motor stroke. A recent review concluded that the 'motor recovery after stroke depends on a variety of mechanisms including perilesional motor reorganisation, use of motor pathways in subcortical structures, use of collateral pathways in the ipsilateral hemisphere, or use of collateral pathways in the contralateral hemisphere, or possibly the development of entirely new motor networks' (19). This means that everything is possible, but all these possibilities need to be explored to improve our knowledge for future application in rehabilitation efforts.

Our own experience is limited, and therefore we would like to give a few examples from other authors. Weiller, who began investigating the reorganisation of the human motor system in the early 90s, concluded from the findings of his group (47), which were based on investigations performed in the chronic state after the attack, that the pattern of reorganisation differs in individual patients depending on the location of the lesion.

Whereas changes in both the damaged and the undamaged hemisphere can be observed, ipsilateral activation of motor cortex is consistently found to be stronger for movement of the paretic fingers after recovery from stroke, whereas movements of the unaffected hand (as in normal subjects) were accompanied mainly by activation of the contralateral cerebral cortex. In addition to stronger intensity, the spatial extent of activation in motor cortex was enlarged, and activation on the ipsilateral side was also seen in premotor and insular cortex. These results indicate that recruitment of ipsilateral cortices plays a role in recovery.

An alternative motor task (thumb opposition) only inconsistently caused ipsilateral sensorimotor activation, and made the role of the ipsilateral motor pathway controversial. Ipsilateral activation was seen in the most severely impaired patients and nonrecovered patients showed stronger ipsilateral and contralat-

eral activation during passive movements than controls (48), indicating that recovery of motor function is achieved by a redistribution of activity within a widespread network of parallel-acting motor areas and pathways.

It was demonstrated by the same group (49) that task-oriented arm training increased activation bilaterally in the inferior parietal area, in premotor areas and in the contralateral sensorimotor cortex, suggesting an improved functional brain reorganization in the bilateral sensory and motor systems. Similar results were obtained by fMRI by which an evolution of the activation in the sensorimotor cortex from early contralesional activity to late ipsilateral activity was found (50), suggesting a dynamic bihemispheric reorganization of motor networks during recovery from hemiparesis. The changes in activation patterns after recovery from hemiparesis include also posterior shifts in primary sensorimotor cortex, contributing to modulation and adaptation of widely distributed parts of the cortical network for motor control (51). It was also shown that the overactivation observed a few weeks after a stroke diminishes over time, suggesting compensatory mechanisms appearing even late in the course (52). Ipsilateral cortical recruitment seems to be a compensatory cortical process related to the lesion of the contralateral primary motor cortex; this process of compensatory recruitment will persist if the primary motor cortex is permanently damaged. If, on the other hand, the damage is transient and the motor cortex is morphologically spared, the ipsilateral recruitment will reverse and activation will develop that is focussed on the contralateral sensorimotor cortex (53). It must be stressed, however, that these different patterns of activation had no relation to the degree of recovery, and in particular that focusing did not imply a favourable outcome.

Our own study was centred on the pattern of activation in relation to the degree of recovery in the early course after stroke. For that purpose patients with subcortical ischaemic stroke underwent PET activation studies with passive finger movements of the paretic hand 1 and 3 weeks after the attack. Improvement of

Table II. Increased (↑) and decreased (↓) task-related flow changes in the course after stroke in the patients group treated with piracetam and on placebo. The piracetam group improved in several language tasks (see Table I).

	Placebo		Piracetam	
	Right	Left	Right	Left
Frontal				
BA 44 (Broca)	-	-	-	-
BA 45 (Broca)	↑*	↓	-	-
Prim. Vocalizing area	-	-	↑*	-
Temporal				
Heschl's gyrus	↑*	-	-	-
BA 41 and 42	-	-	-	-
BA 22 (Wernicke)	↑*	-	-	-
Other				
Suppl. motor area	-	-	-	-

p<0.05

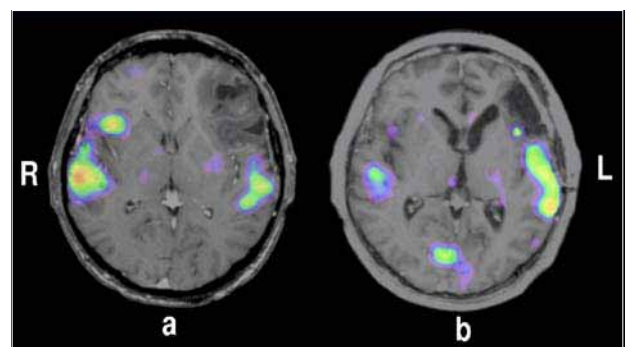


Fig. 2. Interhemispheric compensation with transfer of dominant activation during verb production in a patient with left frontal tumour (a). After tumour resection (b) the activation pattern is normalized with more accentuated activation in left temporal areas, and the speech disturbance is improved.

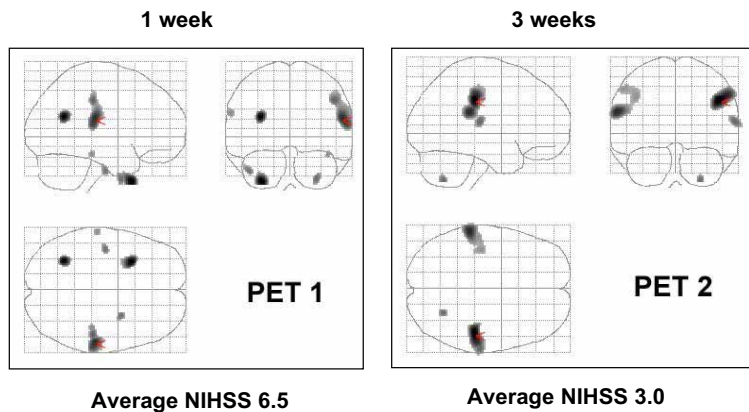


Fig. 3. Change of flow activation pattern during finger tapping in 6 patients with subcortical infarction, with motor improvement bilateral activation scans from 1 to 3 weeks.

motor deficit in this preliminary study on a small group of patients was related to the bilateral activation of the sensorimotor cortex three weeks after the stroke, indicating inter- and intrahemispheric mechanisms contributing to the recovery (Fig. 3). In future studies the reactivation patterns typical for favourable and unfavourable outcome after motoric stroke must be determined. These studies might form the basis for elucidating the effect of rehabilitative measures, including adjuvant drug therapy on these activation patterns and on outcome. Changes in the excitability of the motor cortex were demonstrated for instance with constraint-induced movement therapy, which enlarged the hand areas responding to focal transcranial magnetic stimulation in the affected hemisphere in correspondence to improved motor performance of the paretic limb (54).

In conclusion, functional neuroimaging studies can be used to identify the structures of a bilateral network involved in the recovery of disturbed function and may help in the development and evaluation of rehabilitation strategies.

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