the basic disease mechanism has also recently been implicated in a novel form of hereditary spastic paraparesis due to mutations in another beta-propeller protein, tectonin beta-propeller containing 2, TECPR2 (Oz-Levi et al., 2012). However it is still unclear how increased autophagy relates to iron accumulation. Various basic mechanisms have been implicated in NBIA (altered iron metabolism, fatty acid metabolism, apoptosis, transcriptional regulation, autophagy), but whether abnormal iron deposition is a final common pathway, directly leading to disturbed neuronal dysfunction, or a ‘biomarker’ of NBIA, facilitating disease detection remains to be established (Fig. 1). Identification of novel genetic forms of NBIA, such as the recently reported BPAN provides novel insights to answer this very important question. Better understanding of the disease mechanisms and their role in iron accumulation is essential to define whether novel therapeutic interventions should target iron deposition, or the primary defect (autophagy, fatty acid metabolism, apoptosis etc), secondarily leading to iron deposition, or both (Fig. 1). In neuroferritinopathy, signal intensity in the thalamus showed documented changes over time and good correlation with the clinical rating scale measuring dystonia severity, establishing a link between iron accumulation and clinical presentation (McNeil et al., 2012). Similar studies are urgently needed in other NBIA conditions to determine the natural history of disease and to provide the platform for therapeutic intervention.

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References

Imaging neuronal loss and recovery in compromised but viable brain tissue

Selective neuronal loss, that is necrosis or apoptosis of a portion of neurons in cerebral tissue with grossly preserved architecture (Garcia et al., 1996), is difficult to assess but can seriously impact brain function in patients with cerebrovascular disease. It has been associated with temporary cerebral ischaemia, as in reperfused penumbral tissue (Garcia et al., 1996; Baron, 2005), and with chronic cerebral hypoperfusion due, for example, to atherosclerotic disease of major cerebral arteries or ischaemic heart disease (Yamauchi et al., 2011). Selective neuronal loss may be a significant factor in cognitive impairment and limited functional recovery ability. Conventional diagnostic imaging with CT or MRI does not identify selective neuronal damage (Garcia et al., 1996;...
Sicard et al., 2006). Peri-infarct tissue that displays normalization of 
T2 relaxation time on magnetic resonance images chronically 
after experimental transient cerebral ischaemia—reflective of 
oedema resolution—has been shown to contain areas with 
selective neuronal necrosis (Wegener et al., 2006). On the other 
hand, single photon emission computed tomography (SPECT) 
with 123I-labelled iomazenil, or PET with 11C-labelled flumazenil, 
have the potential to detect tissue with selective neuronal loss 
and distinguish this from fully infarcted tissue (Hatazawa and 
Shimosegawa, 1998). The ligands iomazenil and flumazenil bind 
to central-type benzodiazepine receptors and reduced binding 
therefore reflects neuronal injury in cerebral tissue. In stroke pa-
tients, 123I-iomazenil SPECT and 11C-flumazenil PET have revealed 
reduced benzodiazepine receptor binding in non-infarcted tissue 
that initially was hypoperfused (Saur et al., 2006; Guadagno 
et al., 2008), suggesting that the salvaged ischaemic penumbra 
can still be affected by selective neuronal loss.

After an ischaemic period, mildly affected brain tissue within 
the penumbral zone may recover following reperfusion, for 
example after thrombolytic therapy, and as a result of plasticity. For 
instance, re-emergence of neuronal activation in peri-infarct cor-
tex has been measured with stimulation or task-related functional 
MRI in animal stroke models (Dijkstra et al., 2001) and in patients 
(Jaillard et al., 2005). Functional denervation, depression 
or deterioration of surviving neurons, as well as derangement 
of neurovascular coupling, may lead initially to diminished activa-
tion responses in tissue that is spared structurally. In essence, such 
n neuronal dysfunction without apparent structural damage corres-
ponds to the standard definition of the ischaemic penumbra: func-
tionally inactive, but viable and potentially salvageable tissue. 
Preserved connectivity with healthy brain regions and sustained 
responsiveness to stimuli may enable ensuing functional revival 
of potentially compromised tissue, as has been measured in the 
perilesional sensorimotor cortex of rats recovering from stroke 
(Van Meer et al., 2011). Nevertheless, not all neuronal tissue in 
the penumbra may be recoverable. As previously reviewed by 
Baron (2005), several studies have demonstrated that the pre-
served penumbra may not be entirely without significant neuronal 
damage.

As described above, SPECT or PET enable detection of brain 
areas having selective neuronal loss, and functional imaging tech-
niques allow assessment of the extent to which neuronal function 
is lost, possibly extending beyond structurally damaged cerebral 
tissue as measured by conventional diagnostic imaging. In the 
current issue of Brain, Carrera et al. (2013) present a prospective 
proof-of-principle study with combined acute CT perfusion im-
aging to identify the ischaemic penumbra, with follow-up functional 
MRI to measure cerebral activation, and 15C-flumazenil PET, to 
depict selective neuronal loss in a small group of patients recovering 
from stroke. In line with earlier studies, activation responses 
were measured in preserved penumbral tissue at a subacute stage 
(i.e. 1–3 months) after stroke. However, the authors also showed 
that functional activation is essentially restricted to areas without 
selective neuronal loss. This indicates that selective neuronal loss in 
spared non-infarcted tissue may impede neuronal activation and 
possibly influence neurological recovery after stroke. Since func-
tional restoration of mildly affected cortical tissue is believed at 
least partly to underlie reinstatement of functions in patients re-
covering from cerebrovascular disease, it therefore seems critical to 
develop therapeutic strategies to prevent selective neuronal loss in 
these areas. Yet, the underlying mechanisms of injury to specific 
subsets of neurons in hypoperfused or temporarily ischaemic 
tissue, which may differ considerably from pan-necrosis or com-
plete infarction, remain to be elucidated. Vulnerable neurons may 
deteriorate due to direct consequences of brief ischaemia, meta-
Bolic exhaustion as a result of chronic hypoperfusion or diffuse 
microvascular dysfunction, or secondary events such as inflamma-
tion, while the level of such pathophysiological conditions might 
yet spare other neurons, glial cells and vascular structures. Still 
more research is needed to elucidate accurately the pathogenesis 
of selective neuronal injury associated with a cerebrovascular ac-
cident or insufficiency.

Carrera et al. (2013) conclude that neural circuits may not recover 
their normal functional abilities within the salvaged penumbra 
affected by selective neuronal loss. Nonetheless, structural and func-
tional remodelling of preserved peri-lesional tissue could contribute 
to compensation or partial restoration of disturbed functions, con-
ceivably even in the presence of scattered neuronal injury. This 
may involve growth of neuronal elements, through synaptogenesis 
and neurite sprouting, as well as vascular and glial structures, 
through angiogenesis and oligodendrogenesis, providing metabolic 
and structural support to the reorganized neural network. 
Conceivably, selective neuronal degeneration might even play a 
role in the development of remodelled functional networks by elimi-
nation of superfluous or hindering elements. Overall these reorga-
nizational processes may result in reinstatement of initially silenced 
n neuronal circuits or recruitment of alternative neuronal networks. 
Recent studies with resting-state functional MRI in rodent stroke 
models and patients have demonstrated that early loss of baseline 
signal coherence (or functional connectivity) in the intact ipsilesional 
sensorimotor cortex can be followed by restoration of neuronal 
signal synchronization with functionally connected sensory and 
motor regions, in parallel with recovery of sensorimotor functions 
(Van Meer et al., 2010; Golestani et al., 2013).

In agreement with current concepts on neuronal network injury 
and plasticity, pathological as well as restorative processes jointly 
affect surviving tissue that is post-ischaemically reperfused or 
chronically hypoperfused. Recovery of local neuronal function is 
dependent on the interplay between pathological consequences 
and tissue repair, which significantly influences the effect and 
ultimate potential of rehabilitative therapies. Imaging methods 
that allow detection of selective neuronal loss and assessment of 
the functional status of neuronal networks, as described in the 
paper by Carrera et al. (2013), can contribute to improved diag-
nosis and outcome prediction of compromised but viable brain 
tissue in patients with cerebrovascular disorders.

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