

# Brain plasticity and microglia: is transsynaptic glial activation in the thalamus after limb denervation linked to cortical plasticity and central sensitisation?

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## Abstract

Microglia are a subset of tissue-macrophages that are ubiquitously distributed throughout the entire CNS. In health, they remain largely dormant until activated by a pathological stimulus. The availability of more sensitive detection techniques has allowed the early measurement of the cell responses of microglia in areas with few signs of active pathology. Subtle neuronal injury can induce microglial activation in retrograde and anterograde projection areas remote from the primary lesion focus. There is also evidence that in cases of long-standing abnormal neuronal activity, such as in patients after limb amputation with chronic pain and phantom sensations, glial activation may occur transsynaptically in the thalamus. Such neuronally driven glial responses may be related to the emergence central sensitisation in chronic pain states or plasticity phenomena in the cerebral cortex. It is suggested, that such persistent low-level microglial activation is not adequately described by the traditional concept of phagocyte-mediated tissue damage that largely evolved from studies of acute brain lesion models or acute human brain pathology. Due to the presence of signal molecules that can act on neurons and microglia alike, the communication between neurons and microglia is likely to be bi-directional. Persistent subtle microglial activity may modulate basal synaptic transmission and thus neuronal functioning either directly or through the interaction with astrocytes. The activation of microglia leads to the emergence of microstructural as well as functional compartments in which neurokinins, interleukins and other signalling molecules introduce a qualitatively different, more open mode of cell–cell communication that is normally absent from the healthy adult brain. This ‘neo-compartmentalisation’, however, occurs along predictable neuronal pathways within which these glial changes are themselves under the modulatory influence of neurons or other glial cells and are subject to the evolving state of the pathology. Depending on the disease state, yet relatively independent of the specific disease cause, fluctuations in the modulatory influence by non-neuronal cells may form the cellular basis for the variability of brain plasticity phenomena, i.e. the plasticity of plasticity.

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## 1. Plasticity—introductory remarks

The term ‘plasticity’ has come to encapsulate a number of phenomena in which neurons appear to react to changed conditions by using existing connections in different ways or by establishing new connections. In character, this seems to contradict a certain notion of the brain and its neuronal elements, as having a particularly high functional stability

brought about by its dominant mode of cell–cell communication, i.e. neural/synaptic transmission. This mode of cell interaction has long been perceived to be comparatively immediate, highly predictable, fast and temporo-spatially targeted and not subject to any massive qualitative changes. This supposition serves, for example in functional imaging studies, as the implicit basis of structure–function correlations for which an especially high degree of rigidity is assumed.

However, depending on the cellular mechanism investigated, the length of the observation period, and the level of conceptual integration (molecular, cellular, systemic, etc.), plastic behaviour can be seen

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- (a) at the neuronal level, with temporal latencies beyond that of the typical fast action potential, such as exemplified by long-term potentiation (LTP) or long-term depression (LTD);
- (b) in states of brain disease, injury and regeneration, where—often non-neuronal—cell responses evolve over far greater time periods than usually expected for neurons, i.e. days to months or even permanently;
- (c) and during CNS development, when neural stem cells display an unexpectedly broad differentiation repertoire resulting in considerable plasticity [40].

A central tenant in neurobiology holds that changes in the strength of individual synapses underlie changes in behaviour. It is now a matter of debate and research to determine the extent to which neuronal out-put and the associated behavioural manifestations are subject to glial modulation. There is increasing evidence that glial cells participate in the emergence of plasticity in a wide temporal window: fast and 'online' in direct communication with neurons, or long-lasting to permanent in cases of chronic neuronal disturbance. Protracted glial responses appear to be particularly relevant in brain pathology. In contrast to neurons, that during brain pathology are frequently lost or whose functioning becomes severely compromised, glial cells become 'activated'. The definition of 'activation' is somewhat fluid as it reflects the sensitivity of the detection method used. Generally, however, glial activation manifests itself in the expression of numerous cell regulatory molecules and assumption of new or additional functions, many of which may have a direct bearing on the efficacy of synaptic transmission.

In the diseased as opposed to the healthy brain, microglia are particularly interesting because (a) in the normal brain their manifold potential activities are largely suppressed and (b) when activated by a pathological stimulus, microglia—by virtue of being members of the immune system—introduce a more 'open' mode of cell-cell interaction that appears anathema to the tempo-spatially highly targeted nature of synaptic transmission. This review focuses on the secondary activation of microglia that occurs remote from the primary sites of tissue pathology. Its potential relevance for the emergence of plasticity in the neocortex and possible link to the phenomenon of diaschisis, i.e. lesion-induced associative changes ipsilateral or contralateral to the lesion, will be discussed.

## 2. Neurons alter the functional state of microglia

Microglia are the brain's resident tissue macrophages and originate from the bone marrow for review see: [7]. During CNS development, their numbers increase

regionally and temporally, coinciding with the occurrence of programmed cell death [68]. In the mature healthy brain, their number is markedly reduced, and remains at about 5–10% of the total glial cell population, but then gradually increases with aging [63,106]. In the normal 'resting' condition, microglia lie scattered throughout the grey and white matter and are characterised by a richly ramified morphology. The role of resting microglia has been difficult to address, since most experimental designs disturb this resting state. It seems, however, that, based on *in vitro* observations, microglia could potentially serve trophic functions for neurons [32,49,56]. Following brain injury or neuronal lesion, microglia undergo transformation in a graded fashion. They lose their highly ramified morphology, change their immunophenotype and start to proliferate and migrate (for review: [7,58]). In case of neuronal cell death, they may fully mature into phagocytic macrophages. With the advent of more sensitive detection techniques, it has become possible to observe their involvement at the earliest stages of different types of neuronal injury some of which do not lead to nerve cell death. In fact, physiological changes, such as osmotic stress, may activate microglia as can be observed in the pituitary gland [64]. First signs of microglial activation *in vivo*, such as the *de novo* expression of lectin binding sites and messenger RNA for certain isoforms of the amyloid precursor protein (APP) or ion channels have been observed within minutes and hours [4,76,14]. Fast signal pathways from neurons to microglia must therefore exist. Putative mechanisms are neuronally-triggered changes in ion milieu, such as the local increase in potassium [59]. In certain functional states, microglia lack the outwardly rectifying potassium channel and, therefore, may be particularly sensitive to increased extracellular potassium concentrations [14,15,53,54]. Likewise microglia have purinergic receptors and enzymes involved in the turnover of ATP [53,94]. Importantly, the ability of microglia to respond to changing potassium levels or common co-transmitters, such as ATP, is dependent on whether they are resting or activated [14,69,74,103]. Therefore, the efficacy of these signalling pathways appears to depend crucially on the type and degree of the underlying pathology and thus the amount of glial activation. It should be noted that these neuron–microglial communication routes are not operating in isolation. Astrocytes, too, are active participants and their Ca<sup>2+</sup> waves evoke microglial responses [93]. Further, it is likely that in the healthy brain, too, neurons exert influence over microglia [102]. One mechanism to keep microglia in a quiescent state works via the microglia receptor CD200 and its suppressive ligand, which is expressed on neurons. An active down-regulation of microglial major histocompatibility complex (MHC) expression by healthy neurons has been proposed [79].

In this concept, the activation of microglia in disease would be the result of failing neuronal control.

An important principle of microglial activation is that is not confined to the primary lesion site, but also takes place in the distant retrograde and anterograde projection areas of the lesion neuronal pathway [58]. Thus, there is the induction of ‘projected pathology’ in remote areas. It is perceivable that the occurrence of such secondary responses beyond the primary lesion focus and at certain nodal points of the affected anatomical pathway can interfere with the integrity and function of large scale neuronal networks. This may provide one explanation for the considerable degree of variation between similar appearing focal lesions but marked variability in their functional consequences.

While acute microglial responses are now well characterised, there are also indications that microglial activation can be far more persistent than previously thought. A sustained presence of activated microglia has been described following peripheral inflammatory nerve lesion with concomitant changes in nociception [113] and in the substantia nigra of patients with parkinsonism due to self-administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) up to 16 years earlier [61]. Also, after reinjury of e.g. lumbar roots glial responses, including that of microglia, become more persistent [47]. Thus in any case of persistent pathological stimuli or a self-perpetuating disease process, activated microglia are likely to be present.

### 3. Do microglia alter the functional state of neurons?

Microglial activation is associated with the expression of various classes of biomolecules. Some of these are in principle capable to alter basal synaptic transmission, leading to synaptic plasticity and thus modulation of neuronal output. Microglia can secrete trophic factors, such as growth factors, which promote neurite formation or exert activity on other glial cells, notably astrocytes [19,65,88,92,110]. At present many of the functions suggested for microglia *in vivo* rest on *in vitro* data and thus are still mostly conjectures that remain to be proven *in vivo*. A particularly useful *in vivo* model without direct brain injury and associated damage to the blood-brain barrier are peripheral nerve axotomy models. They have allowed studying the role of glial cells in neuronal plasticity *in vivo* [1,57]. One important observation has been the close proximity of activated microglia to the somata and the presynaptic terminals of injured neurons. These perineuronal microglia appear to be involved in the removal of synapses (‘synaptic stripping’) from the somata and dendrites of axotomized motoneurons, though the degree to which this process is actively initiated by microglia is being debated [1,13]. An indirect effect on the formation of the

astrocyte lamellae that separate the synapse from the injured neuronal somata is another possibility of microglial participation in this microstructural disconnection phenomenon. Some correlative data between microglial activation and terminal sprouting following dentate gyrus deafferentation suggest that the presence of activated microglia is conducive to sprouting which may be supported by microglia-derived insulin-like growth factor-1 [42,109]. Likewise, destruction of the serotonergic input to the striatum causes significant hyperinnervation of the ventral mesencephalon and temporo-spatially coincides with the presence of activated reactive microglia [89]. Similarly, the sprouting of dopaminergic fibres in the wake of striatal injury correlates with the expression of glial cell line-derived and brain-derived neurotrophic factor mRNA in microglia [11]. Bi-directional communication between neurons and microglia can also be observed in models of peripheral sensory axon lesion. Here, the nerve growth factor NGF has been shown to attenuate some of the axotomy-induced neuronal and glial responses that mostly occur before changes in the primary sensory synaptic terminals can be detected [33]. Such transganglionic changes are not exclusively the result of neuronal degeneration but occur contemporaneously with neuronal growth and sprouting [1], indicating that the interaction between microglia and neurons in pathology is not necessarily always to the detriment of the neuron.

There is now a substantial body of literature, that in essence lists the many products activated microglia produce and secrete. Mostly by extrapolation from *in vitro* data but also some observations in genetically altered animals, many of these secreted factors are neurotoxic and thus could be mediators of excitotoxic neuronal injury [5,7,21,22,70,72,91,107]. Microglia as a potential source of the endogenous excitotoxin and putative pathogen quinolinate has received particular attention. Quinolinate is a selective agonist of *N*-methyl-D-aspartate (NMDA) receptors [99] leading to suggestions that at least under pathological conditions microglia rather than astrocytes increase its concentration to levels that may disturb neuronal functioning [66,96], a mechanism also advocated as one cause of HIV-1-associated dementia [45,112]. Yet, these mechanisms of putative microglial toxicity appear to be finely balanced by the simultaneous up-regulating of enzymes in activated microglia, such as glutathione peroxidase, that may help to counteract excitotoxin-induced oxidative stress [67]. The net effect of microglial activation is the result of the factually reached local concentrations of potential neurotoxin or modulators of neuronal function and the efficacy of other additive or counteracting cellular responses, involving astrocytes and neurons alike [25,80,81]. Thus, simple dichotomous views that equate activated microglia with cell toxicity and other glial cell types with neuroprotection are not appropriate,

as exemplified by the difficulty in understanding the true functional significance of raised quinolinate levels [41].

Since microglia are of mononuclear-phagocyte lineage their activation has by default many similarities with inflammatory immune reactions. This fact is the foundation of the concept of ‘neuroinflammation’, i.e. a local immune response induced by neurons without the recruitment of peripheral immunocytes. Rekindling the older theory of ‘histiogenic autotoxicity’ as a common pathogenetic step in a wide spectrum of brain diseases, the idea of ‘neuroinflammation’ has led to the suggestion that also in neurodegenerative disease, such as Alzheimer’s disease, anti-inflammatory intervention may have beneficial effects [31,71]. Though ‘neuroinflammation’ is clearly different from the inflammatory reactions seen in other organs, a least one proviso has to be made: there is evidence that after some delay blood-borne cells may enter the brain secondarily in areas in which microglial activation has previously occurred [35,75,85,86]. The delayed recruitment is thought to be the consequence of an increased local ‘immune-alertness’ due to the presence of activated microglia, which may lead to a site-directed homing of lymphocytes.

#### 4. Imaging microglial activation in vivo

The isoquinoline PK11195, originally discovered as a compound that partially displaces certain benzodiazepines, such as diazepam, binds to a site that is structurally and functionally unrelated to the central benzodiazepine receptor associated with gamma-aminobutyric acid (GABA)-regulated channels. Particularly abundant in peripheral organs and haematogenous cells, but barely present in the normal CNS, the binding site for PK11195 was named “peripheral benzodiazepine binding site” (PBBS). The PBBS was found to co-precipitate with the outer membrane of mitochondria [2], hence its other name, “mitochondrial benzodiazepine receptor” MBR. However, PK11195-binding is also present in non-mitochondrial fractions of brain extracts, and mitochondria-free erythrocytes [82] while immunocytochemical staining hints to the possible presence PBBS in cell nuclei [44]. Amongst others, the PBBS plays an important role in steroid synthesis and regulates immunological responses in mononuclear phagocytes. The numerous other putative functions of the PBBS, that still have to merge into a coherent theory of its biological role, have recently been reviewed by Gavish et al. [37].

Labelled with carbon-11, the PK11195 can be used for the in vivo measurement of activated glia, and thus for the detection of injury-induced neuronal responses by positron emission tomography PET [12,52,24,78,87,95].

The formal evidence that the PET signal derived from the R-enantiomer of [ $^{11}\text{C}$ ](R)-PK11195 is predominantly

due to the presence of activated microglia can be summarised as follows:

- (a) In vivo studies show that the distribution pattern of increased PBBS expression, as measured by PK11195 binding, matches more closely the distribution of activated microglia than that of reactive astrocytes [23,30,77,90,98]. Some discrepancy, however, still remains: in neurotoxic lesion models, immunoreactivity primarily in and around the nucleus of reactive hippocampal astrocytes was detected by a polyclonal antibody against the peripheral benzodiazepine receptor [60].
- (b) High resolution single cell [ $^3\text{H}$ ](R)-PK11195 autoradiography shows that after peripheral nerve injury in rats without disruption of the blood–brain barrier, the binding is strictly localised to mostly perineuronal cells around the soma of the injured neurons. These cells are immunocytochemically identified as activated microglia with no indication of any astrocytic binding in this model [8]. Nerve lesion models causing neuronal cell death and thus stimulating the transformation of microglia into macrophages do not indicate a further rise in of [ $^3\text{H}$ ](R)-PK11195 binding despite the ensuing more pronounced astrogliosis. Immunocytochemical studies using polyclonal antibodies against the PBBS have shown variable staining of cellular elements, including cell nuclei, but have not demonstrated by means of double-labelling the binding of PK11195 to PBBS or GFAP immunoreactive cells, i.e. astrocytes [8,9,60].
- (c) Combined immunocytochemical-double labelling on the single cell level performed on the same tissue section in experimental animals as well as in human post-mortem brain tissue gives direct evidence for the presence of the [ $^3\text{H}$ ](R)-PK11195 binding sites in microglia cells but not in astrocytes. Importantly, the expression of [ $^3\text{H}$ ](R)-PK11195 binding sites does not require the transformation of microglia into macrophages and binding is found on microglial cells that have largely retained their ramified morphology [8,9].
- (d) Studies of well controlled epilepsy patients with hippocampal sclerosis, a tissue pathology characterised by dense astrogliosis did not reveal any regionally increased [ $^{11}\text{C}$ ](R)-PK11195 signal indicative of an active disease process with the presence of activated microglia [6].
- (e) Likewise, long-established lesions identified as hypointense areas in the MRI and known to be surrounded by reactive astrogliosis do not show an increased [ $^{11}\text{C}$ ](R)-PK11195 PET signal [8,9].

Thus, activated microglia form the primary, if not exclusive, source of [ $^{11}\text{C}$ ](R)-PK11195 signal in vivo.

[ $^{11}\text{C}$ ](R)-PK11195 PET has been used to image active brain pathology in stroke [83], multiple sclerosis [9], herpes encephalitis [18], vasculitis [39] and Alzheimer's disease [17]. As predicted on the basis of animal experimental studies, one observation common to all these conditions is the presence of increased [ $^{11}\text{C}$ ](R)-PK11195 PET signals remote from the primary lesion in areas that may appear structural normal. For example, in stroke patients increased [ $^{11}\text{C}$ ](R)-PK11195 binding is regularly found in the ipsilateral thalamus, indicating the activation of microglia in degenerating projection areas remote from the primary lesion [84] (Fig. 1a–c). This may indicate active, long-term microstructural changes in the thalamus after damage to corticothalamic connections. Likewise, in patients after unilateral herpes encephalitis, the distribution pattern of activated glial cells that emerges over a period of months outlines the entire affected limbic system well beyond the initial lesion focus [18]. Such distributed, neuronally induced glial responses may be one putative correlate of diaschisis, and whereby changes in the projection areas of the lesioned pathway would mediate functional changes in yet further, only indirectly connected brain regions. If indeed such distant but protracted effects of acute lesions influenced functional adaptation, it would have general relevance for the understanding of functional impairment, recovery and rehabilitation.

### 5. Transsynaptic glial activation, cortical plasticity and pain

Limb amputation leads to a profound reorganization of the representational zones of the somatosensory cortex and are a well-known example for the significant plastic properties of cortical structures [73]. This cortical plasticity may be associated with the development of abnormal sensations, such as phantom or referred cutaneous sensations. Different mechanisms for the phenomenon have been proposed. Cortical plasticity may be mediated by intracortical mechanisms, such as unmasking of pre-existing, redundant thalamocortical or intracortical connections or sprouting along these connections [34]. However, there is also evidence that alterations at lower levels of the somatosensory system, such as transneuronal atrophy of the thalamus, may underlie the reorganization of the cortex [50,51]. It has recently been possible to detect increases in the [ $^{11}\text{C}$ ](R)-PK11195 binding in the normal appearing, contra-lateral thalamus of patients who have lost an upper limb between 2 and 23 years ago and where suffering to various degrees from painful phantom sensations [3] (Fig. 1d–f). The findings are interpreted as first evidence that peripheral denervation with long-lasting abnormal

stimuli may evoke a transsynaptic glial response beyond the first-order projection areas of the injured neural pathway. Though formal histological confirmation is still outstanding, the increase in [ $^{11}\text{C}$ ](R)-PK11195 binding in the thalamus but not somatosensory cortex indicates the presence of activated microglia, possibly as a consequence of subtle transneuronal changes. Signaling pathways may involve the aforementioned purinergic receptors [43] or simply follow transient changes of the extracellular potassium, as can be measured in the thalamus following experimental dorsal root transection [59]. Important is the fact that this glial activation occurred transsynaptically and is thus, unlike e.g. the thalamic signals seen in stroke patients, purely driven by altered neuronal activity. This subtle activity-dependent change in the thalamus may at least in part cause the stable, long-term rearrangement of the cortical representational maps (Fig. 2a,b). In the case of patients with amputation the persistent pathological activity may result from the frequently occurring neuromata at the severed nerves ends. Indeed, in one of the studied patient, who had experienced persistent phantom pain for 23 years, recurring neuromata requiring surgical removal were present. This seems to support the hypothesis that neuromata may act as ectopic pacemakers leading to persistent neuropathic pain [27]. With increasing duration of abnormal input, subtle but functionally important structural changes could follow suit. The persistence of abnormal function, such as in neuropathic pain, would then have its cellular basis in injury-induced structural changes along the sensory pathways (for review: [114]). There have been suggestions that neuroinflammation, including the presence of activated microglia, in the spinal cord may be pivotal for the development of hyperalgesia by releasing mediators that alter the functional state of the relevant neurons [26,47,108]. The time course of microglial activation corresponds closely to the emergence of enhanced nociceptive behaviour after perioral formalin injection [16], suggesting a role of microglia in the causation of enhanced nociceptive behaviour. Compounds that modulate activated microglia may, therefore, have therapeutic potential for the treatment of neuropathic pain [10,101]. It has already been mentioned that microglial activation does not have to be transient, particularly if a pathological stimulus persists over a prolonged period of time or in case of reinjury [47,61,113]. Since neuropathic pain does not strictly correlate with the activation of microglia in the spinal cord [20], additional central mechanisms are necessary to lead to the emergence of pain states. Thus, if glial responses, as implied above, are indeed part of a central, pain-associated mechanism of central sensitisation, the long-lasting nature of glial responses could be linked to the chronicity of certain pain states and their relative therapeutic resistance.

Long-lasting transsynaptic changes are well described for example in the visual system. Long-term transneuronal dendritic responses are detectable in the lateral geniculate neurons following transection of the primary visual

afferent pathway [38]. Transneuronal retrograde degeneration of retinal ganglion cells can be seen after lesions of the striate cortex [48]. Closely associated with synaptic loss or synaptogenesis, long-lasting transneuronal

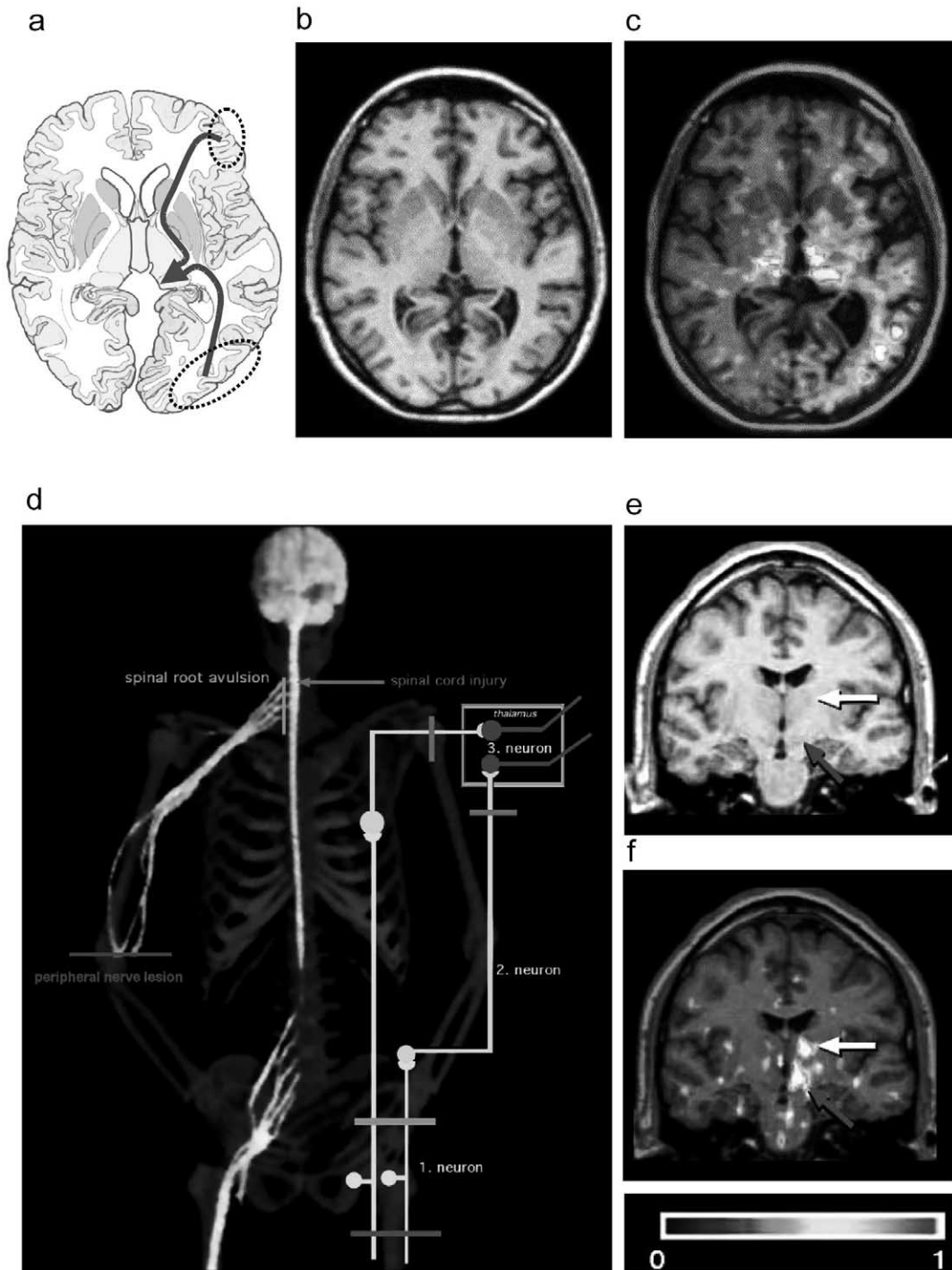


Fig. 1. (a–b) Subacute neuroinflammatory signals, as measured (c) by  $[^{11}\text{C}](R)\text{-PK11195}$  PET and superimposed on a (b) structural magnetic resonance image, are seen in this patient approximately 2 weeks after a cerebral stroke, having affected the cortex in one hemisphere. Increased signal is not only seen in the lesioned cortex, but also in the ipsilateral thalamus as a consequence of injury to the corticothalamic connections. (d–f) Peripheral nerve lesion (d), such as through limb amputation, injures the 1. neuron and (e, f) leads to a contralateral  $[^{11}\text{C}](R)\text{-PK11195}$  PET signal in the thalamus (white arrow), indicating a spread of the glial responses to structurally unaffected transsynaptic projection areas (dark arrow = area of the red nucleus).

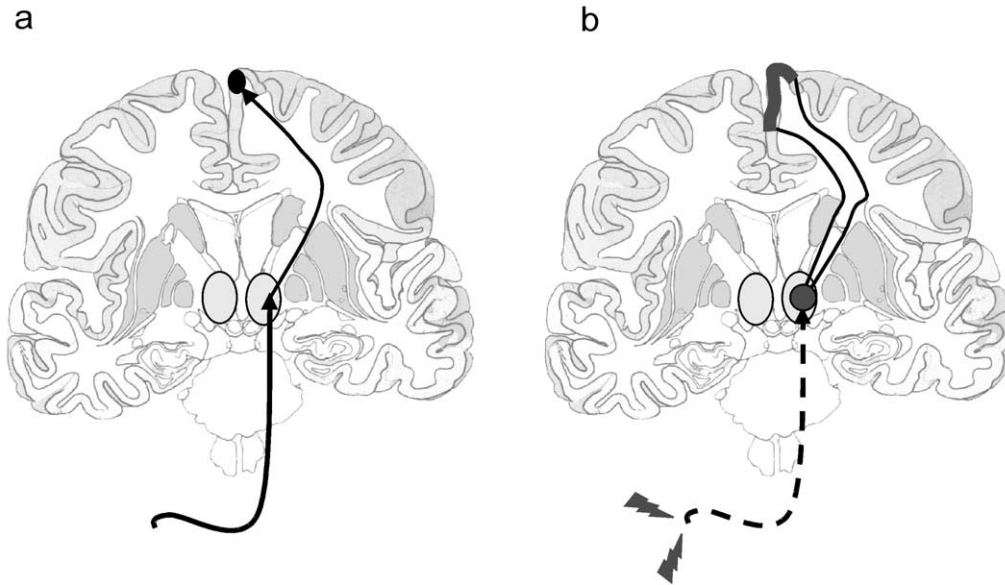


Fig. 2. Hypothetical model of long-term cortical reorganisation: (a) thalamic neurons receive synaptic input from ascending pathways and project to specific areas in the cortex; (b) persistent abnormal input from the ascending pathways, such as in neuropathic pain, leads to long-term structural and functional changes in the thalamus with subsequent lasting changes in cortical representation but without the necessity for cortical rewiring.

changes are present in the hippocampus and entorhinal cortex after experimental lesions or in neurodegenerative disease [28,46,100]. Though not shown formally in all these conditions at least a low-grade glial activation, including microglia, is expected to be present. It has been reported that astrocytes show rapid and transient cortical changes in the density of astrocytic gap junctions in the motor cortex following facial nerve lesions [62]. Transsynaptic microglial activation has previously been observed in the thalamus after intrastriatal nerve cell death induced by quinolinic acid, a model for Huntington's disease [105]. For this model, neuronal hyperexcitation following the removal of inhibitory striatal input has been suggested to be a sufficient trigger for thalamic microglial activation. Similarly, middle cerebral artery occlusion can lead to transsynaptic neuronal changes associated with microglial activation [111].

In summary, the data support the view that plasticity in the cortex is possible because topographical changes in the representational fields of the adult cortex do not necessitate changes in the hard-wiring of the cortex itself [29]. The topographical map and its changes in the mature brain is the emergent property of connections at lower levels, such in the thalamus or in the brain stem. Peripheral nerve injuries lead to changes at these lower levels and may include subtle microstructural rearrangements that support the subsequent representational/functional rededication of the cortical fields. Future research will need to clarify whether the observed glial responses can be viewed as more than secondary, pathological events or whether they represent important adaptive changes that are linked to the plasticity of the plastic phenomena themselves [55,104].

## 6. Methodological and conceptual challenges

At present, any compilations, however selective, of the puzzling variety of glial phenomena tends to be based on *in vitro* work and hence requires conjectures as to the relevance of these findings for the living organism. The mere listing e.g. of soluble factors produced by activated microglia and the many conditions in which they can be found may easily render any concept over-inclusive and makes it difficult to judge their relative importance. Currently, experimental models do not replicate well one of the most important aspects of human brain disease, i.e. chronicity. As exemplified in the case of chronic neuropathic pain, one challenge, therefore, is to develop experimental models that can replicate more realistically the protracted nature of the pathological stimulus and its glial sequelae. It will be in these chronic disease states that inter-glia and glia–neuron interactions are expected to be particularly relevant for the functional out-come, as it is in these conditions that they may override the normally dominant synaptic mode of cell–cell communication. Likewise, it remains to be seen how far models of purportedly purely neural plasticity, such as LTP or LTD, share common features with cellular responses during brain pathology [36,97].

The interaction between neurons is not as exclusive and closed to the participation of non-neuronal cells as long believed. Neuronal transmission is subject to changes in the immediate environment of the neuron and its synapses. The immediate environment is constituted by glial cells that when activated can form normally absent, microstructural as well as functional compartments in which neurokinins, interleukins and other signalling

molecules introduce an apparently less targeted, open mode of cell–cell communication. Importantly, however, this ‘neo-compartmentalisation’ is a strictly site-directed: glial/microglial activation occurs in a meaningfully confined fashion along defined neural pathways, i.e. in remote projection areas and transsynaptic locations. Dependent on the nature and the time frame of the activating stimulus, such secondary glial/microglial activation beyond the primary lesion area may affect important nodal points of a large-scale neuronal network, interfere with its integrity and function and thus lead to diaschisis as a form of ‘hidden disconnection’.

One further consequence of these observations is that because of the de novo emergence of new compartments, the pharmacology of the normal brain cannot be applied to the pharmacology in pathology without significant modifications. Lastly, a major challenge will be to conceptualise the fact that non-neuronal mechanisms show marked plastic changes themselves that have yet to be linked to the behavioural output.

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