Mechanisms of post-stroke fatigue

William De Doncker[1], Robert Dantzer[2], Heidi Ormstad[3], Annapoorna Kuppuswamy[1]

[1] Institute of Neurology, UCL, UK

[2] Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, Texas

[3] University College of Southeast Norway, Norway

Corresponding author

Dr Annapoorna Kuppuswamy

Institute of Neurology,

Box 146, 33 Queen Square

London WC1N 3BG

Email: a.kuppuswamy@ucl.ac.uk

Telephone: 02034488746

Introduction

Stroke is a leading cause of disability [1], with increasing incidence [2] and higher survival rates [3], set to make management of long term consequences of stroke, one of the biggest challenges of the future. Of the many sequelae of stroke, the least understood, most difficult to manage and that which has significant impact on daily life are chronic affective symptoms such as fatigue, pain and mood disturbances [4–6]. There is an urgent need to understand the underlying biological mechanisms of chronic affective symptoms to develop evidence based management strategies and possibly even treatments. In this review we focus on post-stroke fatigue, a common debilitating symptom that has significant implications for morbidity, disability, quality of life and mortality [4–6]. Management of fatigue has been identified by stroke survivors as their top unmet need [7–9] and is a top priority for further research [10]. Fatigue affects a significant percentage of stroke survivors, ranging from 25% to 85%, the large variability a result of the definition and the scale used to measure fatigue, [11–13] including those with mild strokes and little disability [14]. Here, we review recent developments in our understanding of potential triggers for fatigue after stroke, mechanisms that might perpetuate and maintain fatigue in the long term and theoretical models of post-stroke fatigue that might usefully inform future research into post-stroke fatigue.

How do we define and measure fatigue?

Fatigue is a term that is instantly recognisable and understood by all, however, defining fatigue for purposes of quantification and comparison across individuals is notoriously difficult. The difficulty is partly a result of inability to distinguish between the phenomenon of fatigue and its impact. Despite difficulty in defining fatigue, one of the key differences between physiological and pathological fatigue is its resistance to rest and the report of post-stroke fatigue being a distinctly different experience from pre-stroke 'normal' fatigue [15]. Beyond these distinctions, there is little consensus on a definition for post-stroke fatigue. Several attempts have been made to capture the felt experience of fatigue [16–18]. "Fatigue is a multidimensional motor-perceptive, emotional and cognitive experience" [16]; "Fatigue is a feeling of lack of energy, weariness, and aversion to effort" [17]; "decrease or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, an overwhelming feeling of exhaustion, which leads to inability or difficulty to sustain even routine activities and which is commonly expressed verbally as a loss of drive" [18]. Whilst definitions based on felt experience define fatigue from a stroke survivors' perspective, others have attempted to define fatigue from a mechanistic perspective [19,20]. "Pathological fatigue

is, thus, best understood as an amplified sense of normal (physiological) fatigue that can be induced by changes in one or more variables regulating work output. Fatigue could develop during a disease because of dissociation between the level of internal input (motivational and limbic) and that of perceived exertion from applied effort" [19]. "A plausible mechanism of post-stroke fatigue wherein inflammation, the commonest cause of fatigue in neurological conditions, sets in motion a series of changes that include alterations in sensorimotor processing such as sensory prediction associated with effort mechanisms leading to chronic fatigue in stroke survivors" [20]. Little has been done to understand the neurobiological basis of chronic post-stroke fatigue beyond attempting to define it mechanistically, and the only validated tools available to measure fatigue are in the form of questionnaires. The most commonly used scale is the Fatigue Severity Scale [4,5,11,13,21–25] with Neurological Fatigue Index [26], Fatigue Assessment Scale [27,28] and Multidimensional Fatigue Inventory [29–32] also used in several studies. These questionnaires capture both the multi-dimensional nature of fatigue and its impact on daily life. The information captured by the questionnaires and the above definitions allow us to develop plausible mechanistic hypothesis for chronic post-stroke fatigue. The repeated references to 'effort' in the definitions, and effort related statements in the questionnaires, suggest that post-stroke fatigue may be a disorder of effort. We elaborate on evidence that might support this hypothesis in later sections of this review.

Incidence, overlap and impact of post-stroke fatigue

Fatigue after stroke is highly debilitating, with a significant impact on return to work and a major effect on economy [33]. Several studies have documented the rates at which fatigue is reported in stroke survivor populations, which ranges from 25% to 85% [13]. There could be several contributing factors for the reported differences in incidence. Use of different fatigue scales that measure different aspects of fatigue, combined with a lack of consensus on a 'cut-off' point that differentiates the low from high fatigue are limiting factors. Nevertheless, examining the incidence and overlap of fatigue with other affective symptoms could potentially inform our knowledge about origins of fatigue and possibly even the mechanisms of long-term fatigue. Reports of fatigue six months post-stroke ranges from 40-70% [4,12,23,34–36] of which anywhere between 29-87% suffer from post stroke depression [4,9,11,25,37]. A further 33-62% also report sleep problems [4,12] whilst 50-60% suffer from symptoms of pain [4,38]. Post-stroke anxiety was also correlated with fatigue, but after controlling for depression, the association was non-significant [39]. The picture is one of a complex incidence with significant overlap with other affective symptoms. This has previously led to mistaken belief that post-stroke fatigue may be secondary to other primary disorders, however, recent work has highlighted

the primary occurrence of fatigue after stroke [40], for example, almost everyone with depression report fatigue, but not all with fatigue have depression [41]. This complex picture of incidence is perhaps suggestive of common origins or partial overlap of pathways that mediate affective disturbances alongside independent mediators of fatigue.

Investigations have also studied the influence of characteristics such as the type of stroke, age and gender on incidence of fatigue, which might provide some clues for origins of fatigue. There is no reported difference in incidence of fatigue between hemorrhagic and ischaemic stroke [12]. Some studies show a positive correlation between degree of fatigue and age, others show no correlation whilst some others report a higher incidence in younger stroke survivors [6,12,13,24,42–45]. The lack of a consistent report of age positively correlating with fatigue is suggestive of post-stroke fatigue being a direct result of stroke as opposed to a general decline in energy levels with advancing age. A pragmatic approach to age and fatigue is that younger stroke survivors have higher expectations of returning to work which may result in higher reports of fatigue [46,47]. Several investigations report higher incidence of fatigue in female stroke survivors [6,12,24,25,30,45,48], however, this association has not been consistently reported in the stroke population [9,11,41,49]. It is unclear why there might be a difference in fatigue prevalence between the two genders. Interpretation of the difference is further complicated by higher prevalence of fatigue in females in the general population [50].

Time line

Further insight into potential mechanisms can be gained by examining the time course of fatigue after stroke. As previously mentioned, cross-study comparison is limited by differences in inclusion criteria, methods of assessing fatigue and assessment at different time points after the stroke. Longitudinal studies report a consistency in fatigue levels over time [4,13,30,34,50] with some studies reporting an increase in fatigue prevalence with time [12,35] and others reporting a decrease in fatigue prevalence from acute stages (1-3 months post-stroke) to 3 months and thereafter remaining stable [30,34]. Post-stroke fatigue can therefore be divided into early and late fatigue, with most studies defining early as up to 2-3 months post stroke (acute stage) and late as being anything over 3 months post-stroke [40,51]. Some stroke survivors suffering from early fatigue continue to suffer high levels of fatigue in the chronic phase while some stroke survivors only report fatigue in the late phase [40,52,53]. However, a common pattern amongst the majority of stroke survivors is that early fatigue is a strong predictor of late fatigue [52]. A differentiation between early and late fatigue might be indicative of

more than a single trigger and possibly several mediating factors that persist beyond the acute stage of recovery following a stroke.

Mechanisms of post-stroke fatigue

The reported experience of a distinctly different type of fatigue post-stroke, and the development of fatigue in later stages in some, but not other stroke survivors indicates that post-stroke fatigue may not be a non-specific reaction to an insult to the brain but a direct result of the stroke. Here, it is worth reiterating that the majority of stroke survivors report fatigue in the first few weeks after stroke, which is thought to be a general non-specific reaction to a major disruptive event, hospitalisation and re-adjustment to life after stroke. However, the more debilitating symptom is fatigue that fails to resolve (or manifests) several weeks after stroke which is thought to be a stroke related sequel. To identify potential stroke resultant factors that might lead to fatigue, one needs to consider both the direct tissue damage and biochemical imbalances caused by stroke.

Lesion location

The relationship between lesion location and post-stroke fatigue (PSF) remains controversial [9,18,48,51–53,53–55]. The consensus is that lesion location is not determinant of development of fatigue [9,11,30,41,49,56], however some studies suggest there may be a higher incidence of fatigue in sub-cortical strokes when compared to cortical strokes [18]. Sub-cortical strokes may be further broadly classified as basal ganglia and cerebellar strokes, with basal ganglia strokes more likely to give rise to fatigue possibly due to disturbances in the limbic-motor integration networks [48,57]. There isn't enough information available about detailed distribution of cortical lesions and the incidence of fatigue, however, any lesion to attention networks could result in fatigue, as poor attention may be a key element of high effort, a feature of fatigue, as described later in the review [58]. Posterior cerebral artery strokes resulting in thalamic and brainstem lesions have previously been associated with high levels of fatigue. High fatigue in posterior artery strokes may be a result of poor attention mediated by lesions in attentional networks including the ascending reticular activating system, the lenticular, hypothalamic and thalamic nuclei [18,50]. Some authors investigated the difference in incidence of fatigue based on type of lesion. Patients with large vessel stroke experienced greater fatigue than small vessel involvement [59], whilst other studies report an association with cerebral microbleeds [60]. Those with stroke reported greater fatigue than transient ischaemic attack (TIA) despite minimal impairment [14]. An association was seen between fatigue and white matter lesion [61]. These

findings suggest that the presence of a brain lesion rather than post-stroke disability or vascular risk factors might be important in the aetiology of PSF. Furthermore, small vessel disease and development of PSF remains controversial. Whether lesion location significantly influences the development of PSF is still an open question and future studies will benefit from a systematic anatomical correlation of lesion location with fatigue incidence and severity.

Pro-inflammatory response in the acute phase and subsequent fatigue

In a systematic review published in 2012 and based on examination of the literature until the last trimester of 2010, Kutlubaev and colleagues [51] conclude that biological factors probably play a major role in post stroke fatigue. The mechanisms remain uncertain when looking at possible involvement of stroke-induced alterations in Hypothalamic-pitutary-adrenal (HPA) axis and in neurotransmitter systems. In a more recent systematic review, Ponchel et al [62] propose that inflammatory factors appear to play a role although it still needs to be confirmed. Inflammation is well known to be associated with fatigue. Several mechanisms have been proposed for this association (64). Inflammation is mediated by the production and release of proinflammatory cytokines that take place in the brain during stroke because of the peripheral blood mononuclear cells and is amplified by resident macrophages, known as microglia [63]. In addition, inflammation can propagate from the brain to the periphery and vice versa by various communication mechanisms [64]Brain proinflammatory cytokines can act on neurotransmitters such as serotonin and dopamine by several mechanisms including alterations in synthesis, packaging in microvesicles, release, and re-uptake. These mechanisms have been mainly studied in the context of inflammation-induced depression [65]. Inflammation can also induce oxidative stress which, if anti-inflammatory and antioxidant processes are deficient, can lead to neurodegeneration that affects primarily dopaminergic neurons in the meso-striatal and mesolimbic pathways [66]. Inflammation can also activate the kynurenine pathway that, in the context of activated microglia and ongoing neuroinflammation, favors the formation of neurotoxic kynurenine metabolites to the detriment of neuroprotective kynurenine metabolites, and therefore enhances further the risk for neurodegeneration. In this section we will examine the evidence supporting the involvement of each of these mechanisms in stroke-associated fatigue.

Inflammation and fatigue

There is cumulative evidence for an inflammatory reaction in acute ischemic stroke (AIS), indicating important interactions between the nervous and immune systems [67,68] . Cytokines are upregulated in the brain after stroke, and are expressed not only in invading immune cells, but also in glial cells

and neurons [69]. Brain inflammation caused by the stroke episode does not remain local. As mentioned in the previous paragraph it propagates to the periphery. Peripheral inflammation preceding and following a stroke episode has potent modulatory effects on the pathology of stroke. As inflammation measured by peripheral concentrations of CRP and cytokines in serum plasma depends on both pre-existing inflammatory clinical status related to e.g., atherosclerosis and cardiovascular disease and propagation of brain inflammation to the periphery, the results of clinical studies on the relationship between the inflammatory response following AIS and infarct volume [70–78] and stroke subtype [73] are likely to be very variable. The role of the cytokines involved thus remain unclear, and whether post ischemic inflammatory responses are deleterious or beneficial to brain recovery is still a matter of discussion [79,80]. A study, in which the serum levels of 13 cytokines were evaluated in blood samples taken from 45 acute stroke patients (within 72 h of stroke onset) and 40 healthy controls [81], showed for instance significantly higher levels of IL-1ra, IL-6, IL-8, IL-9, IL-10, IL-12, IL-18, and CXCL-1, in stroke patients. The authors concluded that this evidence suggested an early pro-inflammatory response and an early activation of endogenous immunosuppressive mechanism following stroke.

Considering fatigue as a dependent variable in the relationship between stroke and inflammation still adds to the complexity. Despite these difficulties, Ormstad and colleagues investigated the association between PSF, post stroke depression (PSD), stroke type, infarct volume, laterality, and the levels of various cytokines [82,83]. PSF and PSD were measured using the Fatigue Severity Scale (FSS) and Beck Depression Inventory, respectively, at 6, 12, and 18 months after stroke onset. The results indicated a role for the post stroke pro-inflammatory response in the appearance of PSF. The finding that IL-1β seems to be a predictor of PSF [82] suggests fatigue after stroke could be part of what has been described as inflammation-induced sickness behavior [84]. Animal models of stroke support this possibility. For instance, Kunze et. al., [85] showed that experimental stroke in Lewis rats resulted in behavior consistent with depression whilst Wistar and Sprague-Dawley rats exhibited sickness-like behavior including fatigue-like behavior. The role of genetic factors has also been taken into consideration in clinical studies. For instance, Becker and colleagues [86] showed that single neucleotide polymorphisms in the gene coding for the interleukin-1 receptor antagonist and the gene coding for TLR4 were associated with high and low fatigue respectively. However, the small size of the sample (n=39) precludes any definitive conclusion.

A possible neurochemical mechanism for cytokine-mediated fatigue, as discussed earlier could be due to reduced capability for 5-HT synthesis. However, the ineffectiveness of serotonin reuptake inhibitors on post-stroke fatigue [87] may rule out serotonergic pathways as a source of fatigue. Hypodopaminergic activity induced by inflammatory cytokines could potentially be the source of

cytokine induced fatigue [88,89]. An association between serum cytokines and PSD was not found, despite numerous reports of an association between PSD and PSF [83]. Recent hypotheses suggest that glutamate might be the source of affective symptoms related to depression [90,91] but may not mediate fatigue unrelated to depression.

Inflammation-mediated activation of the kynurenine pathway and fatigue

Inflammation can induce neurotoxicity by up-regulating the indoleamine 2,3-dioxygenase (IDO) enzyme (which catalyzes the rate-limiting step in the synthesis of kynurenine (KYN) from tryptophan (TRP)) in multiple central and peripheral cell types [92,93]. Activation of IDO can be measured by increased plasma/serum kynurenine over tryptophan ratio. Kynurenine by itself acts as a ligand of the aryl hydrocarbon receptor, which generates regulatory T cells. The evidence in favour of such a mechanism in PSF is still weak. One study in particular reported reduced percentage of circulating regulatory T cells combined with increased systemic Th17 and pro-inflammatory cytokines and reduced anti-inflammatory cytokines [94]. In addition, interferon–gamma, the cytokine primarily responsible for up-regulating IDO was not higher in stroke [81] when compared to healthy controls. Kynurenine produced in the brain in response to injury or transported from the periphery is further metabolized into the neuroprotective kynurenine metabolite kynurenic acid (KA) by kynurenine aminotransferase, and the neurotoxic kynurenine metabolites 3-hydroxykynurenine (3-OH-KYN), and quinolinic acid (QA) by kynurenine monooxygenase. Activation of microglia, the main cellular source of proinflammatory cytokines in the brain during neuroinflammation, favors the neurotoxic pathway at the same time as it results in the extracellular release of glutamate. Whether microglial activation and the formation of neurotoxic kynurenine metabolites is involved in PSF is not clear. A few studies based on variations in plasma levels of KYN metabolites indicate activation of the kynurenine pathway could play a role in post-stroke sequelae [95–98]. Darlington et al. showed increased TRP catabolism after stroke, and suggest that oxidative tryptophan metabolism contributes to oxidative stress and brain damage [96]. Brouns et al. showed a correlation between KYN/TRP ratio and stroke severity and long-term stroke outcome which did not correlate with KA/3-hydroxyanthranillic acid ratio [95]. Mo et al. showed an up-regulation of IDO activation in ischemic stroke [98]. Ormstad et al., indicated an increase in TRP oxidation and reduced capability for 5-hydroxytryptamine (5-HT) synthesis in the brain following AIS [97].

Ormstad et al., also investigated the mechanisms involved in PSD and PSF by studying the relationship between KYN-pathway activity in the acute ischemic phase and subsequent PSF and PSD in the stroke sample referred in their previous publication [99]. Compared to the other neutral amino acids that compete with tryptophan for entry into the brain, plasma levels of TRP index were significantly lower

in patients with an FSS score of ≥4 than in those with an FSS score of <4 at 12 months. However, in contradiction with the neurotoxic hypothesis the serum levels of KA were significantly higher in patients with an FSS of score ≥4 than in those with an FSS score of <4 at 18 months. This indicates stroke patients with PSF might have a lower bioavailability of TRP in the acute stroke phase. In contrast to PSF, no predictors of PSD were found. These findings suggest that the immune response and IDO activation that follows AIS can predict PSF but not PSD. Interestingly, the TRP index did not correlate with fatigue at earlier time points (6 months) and similarly, another study [100] also showed no correlation between KYN/TRP ratio and fatigue in the very early stages post stroke (1 month). Emerging evidence appears to suggest that early activation of the KYN pathway does not manifest immediately as fatigue and depression, but may have long-term consequences which has led to the proposal of a biopsychosocial model for post-stroke fatigue and depression [101].

Neurophysiological and behavioural perturbations in chronic post-stroke fatigue

A particularly challenging aspect of investigating persistent fatigue is the difficulty in differentiating the causes, from the effects of fatigue. Persistent symptoms such as fatigue result in significant behavioural and neurophysiological changes, which in turn may cause further fatigue resulting in a vicious cycle [101]. Thus, identifying the mechanism that first establishes persistent fatigue is not straightforward. To date, investigations addressing behavioural and neurophysiological underpinnings of post-stroke fatigue have all been correlational studies, which, for reasons stated below, do provide minimal insights into the direction of causality between behaviour, fatigue and physiology. However, causality remains to be confirmed by interventional studies aimed at alleviating fatigue.

Physical deconditioning is a common sequela after stroke and is believed to trigger PSF. Physical deconditioning results in fatigue and subsequently, avoidance of physical activity. This further deteriorates deconditioning and can lead to more fatigue [102]. A recent systematic review however failed to find an association between fatigue and any measures of physical activity or fitness [103]. Both motor and cognitive deficits are seen in post-stroke fatigue. In the first year after stroke, in the absence of any obvious motor deficit, PSF was associated with poor attention and executive function as measured using phasic attention test and modified stroop task [104]. Whilst fatigue correlated with attentional and executive function, neither correlated with lesion location. Another independent investigation [105] confirmed poor executive and memory functions in high PSF in the first 6 months after stroke. They also showed that side and size of lesion did not correlate with presence of PSF. Despite subtle differences between the two investigations in terms of PSF definition and tests used to

measure cognitive function, both investigations suggest that at 6 months post-stroke, cognitive impairment correlates with fatigue with no obvious link to the lesion itself.

Several studies show that PSF is not correlated with motor deficits. However, a closer look at these investigations show that tests used to identify motor deficits are normally questionnaire based scores of activities of daily living such as Barthel index, Rankin scale and National Institutes of Health Stroke Scale (NIHSS) [25,28,34,46,56,86,104,105]. Some studies use laboratory based tasks to measure motor function such as action research arm test (ARAT), nine-hole peg test (NHPT), grip strength [106] and scales such as Fugl-Meyer [107]. These measures, although useful to identify gross motor limitations relevant to daily life, are not accurate measures of motor impairment. A recent investigation showed in evenly matched, minimal motor functional deficit high and low PSF groups, there was a significant reduction in ballistic movement speeds in the affected limb of the high fatigue group [108] whilst no difference in simple reaction times, attention and information processing speed was observed. The significantly slower ballistic speeds did not reflect on laboratory test scores, such as the NHPT times, possibly because tasks such as NHPT capture not only movement velocity but other features such as dexterity. Does this mean that after all, PSF is related to motor impairment? The above investigation did not determine if those with slower movement speeds were capable of achieving higher speeds. It could be that in the task, one chose to move slower than their maximum speed. Those with slower movement speeds also reported heaviness of the affected limb [109], possibly a central sensory processing problem, which in turn may have led to choosing lower movement speeds. Those with lower movement speeds also exhibited low motor cortex excitability [106]. It is unclear if the two findings have a direct relationship as it has previously been shown that motor cortex excitability does not encode movement speeds [110], however is crucial in motor learning involving movement speeds [111]. Low motor cortex excitability was also significantly correlated with high levels of PSF, but interestingly, voluntary activation, a measure of excitability of structures upstream of motor cortex such as secondary motor areas, was not significantly related to fatigue. Thus, PSF appears to be associated with behavioural [108] and perceptual [109] sensorimotor deficits with some underlying neurophysiological [106] perturbations in the sensorimotor pathway.

Do any of the above findings suggest a causal role for motor and cognitive, behavioural and neurophysiological deficits, in development of PSF? The attention and executive impairments seen in PSF are global. Structural and physiological changes remote to the site of lesion resulting in global attentional and executive impairment is a well-documented phenomenon after stroke. However, without further investigations the above correlations between fatigue and attention/executive

impairment cannot be interpreted as being causal to fatigue., fatigue related sensorimotor behavioural, physiological and perceptual findings are confined to the affected hemisphere. Should they be a consequence of fatigue, one would expect a more global effect on behaviour, hence there may be a causal role for sensorimotor alterations in development of fatigue. A small pilot interventional study reported significant benefits to using cognitive behavioural therapy and graded exercise [112] for PSF. However, the effect size was not great enough to suggest that the intervention had targeted the underlying causal neural perturbations, but rather may have succeeded in compensating for some of the fatigue resultant behavioural changes. Moreover, the length of follow-up was not sufficient to determine fully the long-term effects of the intervention.

Active Inference based theoretical model of post-stroke fatigue [20,113–115]

Poor attention, slower processing speed, diminished memory, reduced movement speed and perceived limb heaviness: how might the above deficits give rise to fatigue, when no seemingly direct cause for fatigue such as sustained exertion exist? To answer this, we must first understand how sustained exertion might give rise to fatigue. With sustained activity, performance in the task drops and importantly, subjects report fatigue, or more precisely, the need for higher effort to maintain task performance and at task failure, the inability to exert required effort to perform the task [116]. It is also well established that task performance and report of fatigue are not correlated [117]. Hence, the notion of higher effort is inextricably linked to fatigue whilst drop in task performance itself may be seen as behavioural consequence of fatigue. A dissociation between task performance and fatigue, with a closer link between effort or 'estimated action cost' and fatigue, is indicative of a possible causal link between estimated action cost and fatigue. A recent review discussed how the low motor cortex excitability, reduced movement speed and perceived limb heaviness could underpin aberrant 'estimated action cost' or effort. Aberrant effort results in higher than normally required effort for everyday tasks [20]. Persistent high effort for simple tasks gives rise to fatigue. This fits well with the clinical symptoms of PSF, such as, fatigue without prior activity, fatigue that does not respond to rest and fatigue that limits everyday activities.

Effort is a perceptual inference that has its origins in intention (efferent information) and is modulated by feedback (afferent information). The active inference theory of sensorimotor control integrates efferent and afferent inputs to explain movement initiation and motor control [113] and provides a framework within which effort, as defined above may arise [118]. The active inference theory of sensorimotor control postulates that the (efferent) output from cortico-motor system is in the form

of sensory (proprioceptive) predictions and (afferent) input from the somatosensory systems is in the form of sensory (prediction) errors. For a movement to be initiated, i.e. sensory predictions to be fulfilled, ascending sensory errors must not be attended to and to maintain status quo, sensory errors must be attended to. This property of altering precision of sensory errors is known as 'sensory attenuation'. It has been postulated [118] that in post-stroke fatigue, inference of high effort could be the result of poor sensory attenuation. In the context of muscle contractions, the inability to suppress ascending prediction errors is inferred by the brain as needing more than the estimated effort, to perform the contraction. The motor cortex encodes prediction errors as shown by a suppression of sensory attenuation when motor cortex excitability is artificially reduced using non-invasive brain stimulation [119]. The observed reduction in motor cortex excitability in stroke survivors with high fatigue [106] further suggests poor sensory attenuation may be the mechanism by which fatigue arises. Evidence from other pathological conditions implicating dopaminergic systems in poor sensory attenuation [115] combined with post-stroke fatigue related molecular disturbances and pre-clinical work in muscle metabolism post-stroke [120,121] lend support to both central and peripheral mechanisms playing a role in poor sensory attenuation.

Conclusion

Post-stroke fatigue is highly prevalent and has a significant impact on lives of stroke survivors. Here we summarise our current knowledge about possible causes of post-stroke fatigue. Preliminary evidence supports the idea of stroke triggered early biochemical imbalance resulting in altered homeostasis, leading to beliefs about estimated action cost that manifest as behavioural changes which fail to reverse in the long term presenting as chronic post-stroke fatigue. Understanding mechanisms of post-stroke fatigue is a relatively new field of study and several outstanding questions need to be addressed by future investigations.

Early changes in the biochemical environment after stroke has been implicated in development of a whole host of affective symptoms including fatigue, some of which have been discussed here. It is as yet unclear if there are biochemical imbalances in the chronic phase that might account for fatigue. Further work is also required to identify what biochemical signatures distinguish fatigue from depression. A limitation of current investigations is that all studies rely on biochemical markers in the plasma, which is not necessarily a reflection of the biochemical environment in the brain. Cerebrospinal fluid markers of fatigue will help establish more accurately fatigue specific triggers.

The main behavioural consequence of fatigue is a significant reduction in self-initiated voluntary behaviour, possibly driven by altered effort calibration as discussed previously. Identifying specific

motor and non-motor behaviours that are affected by effort mis-calibration might be helpful in developing interventions for managing fatigue. However, it is imperative that we first establish that the identified behavioural alterations are mediators of fatigue and not merely a result of fatigue. Future work must also concentrate on developing and validating frameworks within which one can explain fatigue, such as the one proposed here, the active inference based framework of fatigue.

In summary, fatigue is a complicated phenomenon with several contributing factors, most of which are poorly understood. Here, we have attempted to bring together several lines of enquiry and proposed a potential unified framework of fatigue.

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