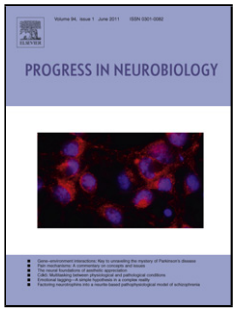

Network neuroscience of apathy in cerebrovascular disease

Jonathan Tay, Danuta M. Lisiecka-Ford, Matthew J. Hollocks, Anil M. Tuladhar, Thomas R. Barrick, Anne Forster, Michael J. O'Sullivan, Masud Husain, Frank-Erik de Leeuw, Robin G. Morris, Hugh S. Markus

PII: S0301-0082(20)30040-X

DOI: https://doi.org/10.1016/j.pneurobio.2020.101785

Reference: PRONEU 101785

To appear in: *Progress in Neurobiology*

Received Date: 10 September 2019

Revised Date: 26 February 2020

Accepted Date: 3 March 2020

Please cite this article as: Tay J, Lisiecka-Ford DM, Hollocks MJ, Tuladhar AM, Barrick TR, Forster A, O'Sullivan MJ, Husain M, de Leeuw F-Erik, Morris RG, Markus HS, Network neuroscience of apathy in cerebrovascular disease, *Progress in Neurobiology* (2020), doi: https://doi.org/10.1016/j.pneurobio.2020.101785

Network neuroscience of apathy in cerebrovascular disease

Jonathan Tay [a], Danuta M. Lisiecka-Ford [a], Matthew J. Hollocks [a], Anil M. Tuladhar [b], Thomas R. Barrick [c], Anne Forster [d], Michael J. O'Sullivan [e], Masud Husain [f], Frank-Erik de Leeuw [b], Robin G. Morris [g], and Hugh S. Markus [a]

[a] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

[b] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

[c] Neuroscience Research Centre, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK

[d] Academic Unit of Elderly Care and Rehabilitation, University of Leeds, Leeds, UK

[e] University of Queensland Centre for Clinical Research, University of Queensland Australia, Brisbane, Australia

[f] Nuffield Department of Clinical Neurosciences & Department of Experimental Psychology, University of Oxford, Oxford, UK

[g] Department of Psychology, King's College London, London, UK

Address correspondence to: Jonathan Tay,

Stroke Research Group, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, R3, Box 83, Cambridge, CB2 0QQ, UK

E-mail: jonathantay193@gmail.com or jt629@medschl.cam.ac.uk

Words: 9145

Figures: 5

Highlights

- A network-based model may be able to describe apathy in cerebrovascular disease.
- Focal network damage, such as in stroke, could lead to network failure and apathy.
- Changes to remote regions or network disconnection can lead to apathy over time.
- Specific subnetworks may underlie motivation-related cognitive functioning.
- Understanding the network basis of apathy could lead to targeted treatments.

Abstract

Apathy is a reduction in motivated goal-directed behavior (GDB) that is prevalent in cerebrovascular disease, providing an important opportunity to study the mechanistic underpinnings of motivation in humans. Focal lesions, such as those seen in stroke, have been crucial in developing models of brain regions underlying motivated behavior, while studies of cerebral small vessel disease (SVD) have helped define the connections between brain regions supporting such behavior. However, current lesion-based models cannot fully explain the neurobiology of apathy in stroke and SVD. To address this, we propose a network-based model which conceptualizes apathy as the result of damage to GDB-related networks. A review of the

current evidence suggests that cerebrovascular disease-related pathology can lead to network changes outside of initially damaged territories, which may propagate to regions that share structural or functional connections. The presentation and longitudinal trajectory of apathy in stroke and SVD may be the result of these network changes. Distinct subnetworks might support cognitive components of GDB, the disruption of which results in specific symptoms of apathy. This network-based model of apathy may open new approaches for investigating its underlying neurobiology, and presents novel opportunities for its diagnosis and treatment.

Abbreviations: SVD = small vessel disease; GDB = goal-directed behavior; WMH = white matter hyperintensities; PFC = prefrontal cortex; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; SMA = supplementary motor area; NAA = N-acetylaspartate; rCBF = regional cerebral blood flow; DTI = diffusion tensor imaging; FA = fractional anisotropy; rTMS = repetitive transcranial magnetic stimulation; CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CRP = C-reactive protein; TMT-B = Trail Making Test part B; BMI = body mass index.

Keywords: apathy, stroke, cerebral small vessel disease, cerebrovascular disease, networks, cognition

1. Introduction

Apathy is a behavioral syndrome that is characterized by a loss of motivation (Marin, 1991). It presents in one-third of all patients following ischemic or hemorrhagic stroke (Caeiro,

Ferro, and Costa, 2013; van Dalen et al., 2013) and is a prominent symptom in sporadic and genetic cerebral small vessel disease (SVD) (Reyes et al., 2009; Tay et al., 2019). The prevalence of apathy may be higher in vascular dementia - a condition that results from the impact of cerebrovascular disease on the brain - when compared to Alzheimer's disease (Bandyopadhyay et al., 2014; Fuh et al., 2005; Hargrave et al., 2000). Furthermore, apathy in itself is a risk factor for incident stroke, myocardial infarction, dementia, and mortality (Eurelings et al., 2018; van Dalen et al., 2018).

Recent research on the fundamental neuroanatomical and neurocognitive mechanisms underlying apathy has broadened our understanding of apathy in cerebrovascular disease and across neurological disorders. Despite this, theoretical work has primarily focused on linking neurodegenerative pathology to apathy, such as in Alzheimer's disease or Parkinson's disease (e.g., Lanctôt et al., 2017; Pagonabarraga et al., 2015). This has left the mechanisms underlying apathy in cerebrovascular disease comparably under-explored. Given the high prevalence of comorbid vascular pathology in neurodegenerative conditions (Iadecola, 2010), insights into apathy in cerebrovascular disease might also prove useful in elucidating brain mechanisms underlying motivation in healthy individuals and apathy across a range of diseases.

We begin by briefly introducing the concept of apathy, as well as challenges in understanding it through current frameworks (Section 2). We then propose a network-based theory to explain the pathogenesis of apathy in stroke and SVD (Section 3). The cognitive mechanisms that may link network damage to apathy are then discussed (Section 4). Next, we explore how apathy might be a predisposing factor for incident vascular disease, as this is an

important methodological consideration (Section 5). Future areas for research are then reviewed (Section 6).

2. Apathy: concept and challenges

Apathy is defined as a loss of motivation that manifests as a reduction in goal-directed behavior (GDB) (Levy and Dubois, 2006; Marin, 1991). This is defined in relation to a patient's previous level of functioning, in order to account for the interindividual, environmental, and sociocultural factors that may influence normative functioning. In addition to reductions in GDB, it is also recognized that there may be other aspects to apathy including emotional blunting, lack of motivation to interact socially and reduced intellectual curiosity (Robert et al., 2018). Other terms used to describe different but related manifestations of apathy in the literature include abulia, athymhormia, and auto-activation deficit (Levy and Dubois, 2006).

Importantly, apathy can be dissociated from depression in cerebrovascular diseases and in other neurological conditions more generally (Oguru et al., 2010; Starkstein et al., 2005; Tay et al., 2019; Withall et al., 2011). A substantial body of evidence suggests that the two constructs, when examined as broad syndromes, are dissociable in terms of neurobiology (Douven, Köhler, Rodriguez, et al., 2017), cognition (Fishman et al., 2018a, 2018b; Lohner et al., 2017), longitudinal trajectories (Caeiro, Ferro, Pinho e Melo, et al., 2013; Withall et al., 2011), and impact on functional outcomes (Hama et al., 2007; Hollocks et al., 2015; Mayo et al., 2009). Comorbidity estimates range between 3.8 - 41.9% (Matsuzaki et al., 2015; Withall et al., 2011), although these vary by population, assessment time, and measures of apathy and depression.

Some behavioral manifestations of apathy may overlap with those seen in depressive disorders. For instance, diminished pleasure and energy, which are symptoms seen in major depressive disorder (American Psychiatric Association, 2013), may resemble symptoms of apathy. This overlap is likely due to the fact that the syndromes of apathy and depression, as currently defined, are collections of symptoms. As a result, overlapping symptoms such as diminished pleasure may share a common neurobiological basis (Cuthbert and Insel, 2013; Husain and Roiser, 2018), although little research has explicitly tested this. Dissociating between apathy and depression, while a clinically important question, is beyond the scope of this review, which will focus on the mechanisms leading cerebrovascular disease to apathy. Reviews on the conceptual and empirical differences between apathy and depression can be found elsewhere (Douven, Köhler, Rodriguez, et al., 2017; Marin, 1991; Starkstein and Manes, 2000).

Several frameworks have attempted to explain apathy in terms of specific neurobiological deficits. The most influential of these is by Levy and Dubois (2006), who proposed, from a theoretical perspective, that the symptoms of apathy can be conceptualized as 'emotional-affective', 'cognitive', and/or 'auto-activation' deficits. It has been proposed that these symptoms arise spontaneously as a consequence of focal damage or disruption to territories within the basal ganglia and prefrontal cortex (PFC), which may constitute a core subcortical-cortical circuit underlying GDB. This framework has guided much apathy research over the past decade, and has been incorporated into proposed diagnostic criteria and several clinical scales (Radakovic et al., 2015; Robert et al., 2018).

Unfortunately, empirical evidence that supports the three separate dissociable constructs proposed by Levy and Dubois (2006) remains scarce. This is especially true regarding apathy in cerebrovascular disease. If apathy is the product of lesions to specific regions of the basal ganglia or PFC, then one would expect a clear relationship between stroke location and the presentation of apathy symptoms. This, however, has proven not to be the case, as lesions are distributed heterogeneously in patients with apathy (Sagnier et al., 2019; Tang et al., 2013; Yang, X.-y. Shang, et al., 2015). Furthermore, meta-analytic evidence suggests that there is no clear relationship between lesion location and the development of post-stroke apathy (Douven, Köhler, Rodriguez, et al., 2017; van Dalen et al., 2013), although this may be partially explained by whole-brain lesion-symptom mapping studies being underpowered to detect such effects.

Other findings also appear anomalous, or difficult to explain, when viewed through this framework. For instance, some patients who are apathy-free during the acute phase of stroke develop it one year later, while other patients with apathy in the acute phase recover after one year (Caeiro, Ferro, Pinho e Melo, et al., 2013; Withall et al., 2011). If apathy develops spontaneously after a focal basal ganglia or PFC lesion, then why would apathy present up to a year later? Conversely, what mechanisms lead to some patients with apathy recovering normal function? These questions make it clear that a classical lesion-deficit model of apathy is unable to explain the full clinical phenotype of the syndrome in cerebrovascular disease.

3. A network model linking cerebrovascular pathology and apathy

We propose that apathy might potentially be better understood as a syndrome caused by damage to large-scale brain networks supporting GDB. This connectionist model is based on

the tenets of graph theory and network analysis (Bullmore and Sporns, 2009), which have recently been able to explain and synthesize an impressive array of neuroscientific data (e.g., Schindlbeck and Eidelberg, 2018). This section will begin with a brief overview of network neuroscience (Section 3.1), followed by a proposal of the network mechanisms underlying apathy (Section 3.2). Evidence to support the hypothesis that apathy is a syndrome of network disruption is then reviewed in stroke (Section 3.3) and SVD (Section 3.4). A discussion of the anatomical subnetworks and cognitive mechanisms underlying apathy can be found in Section 4.

3.1. Fundamentals of network neuroscience

The study of brain networks has been made increasingly more tractable with the application of graph theory. A graph has two fundamental elements: nodes and their connecting edges. In the context of macroscopic whole-brain networks, nodes are typically defined using a parcellation that divides the brain using predefined criteria, such as on the basis of sulci and gyri (e.g., Desikan et al., 2006) or cyto- and myelo-architecture (e.g., Eickhoff et al., 2005), while edges are defined based on the context of the study. For example, studies on structural connectivity can define an edge as the probability that two regions are connected by a white matter tract. In studies of functional connectivity, edges can be defined as the correlation between the time series of two regions (Bullmore and Sporns, 2009).

This graph-based representation of the brain can then be quantitatively analyzed to make inferences based on network topology. Two fundamental network measures are degree and efficiency (Figure 1). The degree of a node is simply the number of connections it has to

other nodes (Figure 1A). High-degree nodes are known as network hubs, which are core elements of large-scale brain networks (van den Heuvel and Sporns, 2013). Due to a large number of connections with other nodes, hubs participate in a diverse set of cognitive functions (Bassett et al., 2009), albeit at an increased metabolic cost (Collin et al., 2013). Hubs can be contrasted with low-degree peripheral nodes, which tend to show more local and specialized patterns of connectivity. A more comprehensive discussion of hubs can be found elsewhere (van den Heuvel and Sporns, 2013).

FIGURE 1 AROUND HERE

Another important network measure is efficiency, which measures the ease of information transfer in a network (Latora and Marchiori, 2001). The shortest path length between two nodes minimizes the number of edges traversed between the two (Figure 1B). The average inverse shortest path length between all nodes in a network is its global efficiency, and is a measure of overall integration in a network. The local efficiency of a node is the global efficiency of a subgraph composed of all first-degree neighbors of that node. The average local efficiency across all nodes is a measure of segregation and specialization. More rigorous mathematical definitions of these concepts can be found elsewhere (Latora and Marchiori, 2001; Watts and Strogatz, 1998). Global and local efficiency are susceptible to neuropathology (Rubinov and Sporns, 2010).

The effects of brain pathology can be described using network models (Fornito et al., 2015). Direct damage to network hubs, such as through focal ischemia or hemorrhage, could lead to apathy. However, cerebrovascular disease may also lead to remote changes that result in apathy. These remote changes can be modeled as network pathologies, of which two are

discussed: diaschisis and transneuronal degeneration. Diaschisis refers to a functional deficit in a region that is connected to a focally damaged area (Figure 1C), which is mediated by a reduction or interruption in the connectivity between the two regions (Carrera and Tononi, 2014). This can be operationalized as reduced glucose metabolism or regional cerebral blood flow (rCBF) in the area of diaschisis, under the assumption that neurovascular coupling (functional hyperemia) is preserved in this region (Baron et al., 1984). Although these functional deficits were once thought to be temporary and reversible, this notion has been challenged by recent evidence suggesting that morphological changes may occur in remote regions directly connected to an infarct (Duering et al., 2015). These changes are also seen in young stroke patients (Schaapsmeerders et al., 2016), suggesting that they are related to stroke and not a different neurodegenerative pathology. Secondary morphological damage is consistent with transneuronal degeneration (Figure 1D), a process by which damage to distant nodes propagates through structural or functional connections (Fornito et al., 2015).

It is important to stress that the interpretation of these measures, as well as the network pathologies described, should be carefully considered in the context of how nodes were defined. For instance, consider two network studies: one using structural magnetic resonance imaging (MRI) to define nodes on the basis of sulci and gyri, another using microelectrode arrays to define nodes on the basis of implanted electrodes. In the former case, each node represents the large-scale organization and dynamics of several millions of neurons, while in the latter, each node can capture the function of approximately three neighboring neurons (Schroeter et al., 2015). It is clear that inferences made on one cannot and should not be applied to the other. This situation is further complicated by the fact that nodes in

macroscopic networks can be derived using data-driven or random parcellations at the group or participant level (de Reus and van den Heuvel, 2013).

The following sections in this review consider the network mechanisms underlying apathy in the context of large-scale macroscopic networks. These are described at resolutions available for conventional MRI or computerized tomography out of necessity, given that the overwhelming majority of apathy research is conducted *in vivo* on humans using these techniques.

3.2. Candidate network mechanisms underlying apathy

The network measures that we have previously described, such as nodal degree and efficiency, allow us to reconceptualize the neurobiological basis of apathy. We propose that the hub nodes of GDB-related networks correspond to the structures found to be associated with apathy across neurological diseases. These include the anterior cingulate cortex (ACC), medial orbitofrontal cortex (OFC), ventral striatum, medial thalamus, and ventral tegmental area (Kos et al., 2016; Le Heron, Apps, et al., 2018). These structures play important roles in the cognitive processes that guide effort-based decision-making in healthy individuals (Le Heron, Apps, et al., 2018), so it is reasonable to suppose that they form a foundation for motivation-related brain networks in humans. Damage to these putative network hubs - such as through focal ischemic or hemorrhagic stroke - can lead to immediate failure of GDB-related cognitive functions, which would then manifest as apathy. This view effectively subsumes the classical lesion-based view of apathy (Levy and Dubois, 2006).

In contrast to hub node damage, peripheral node damage may result in diaschisis or transneuronal degeneration. Based on the connectivity profile of the damaged node, these pathologies can lead to apathy by spreading to a remote hub node, or through progressive damage over time to GDB-related subnetworks. The former case can be illustrated by a hypothetical patient with a focal supplementary motor area (SMA) infarct. SMA shares direct white matter connections with the ACC, a hub node, in the form of branching U-fibers from the corticospinal tract (Nachev et al., 2008; Vergani et al., 2014). These structural connections form the basis of functional interactions between these areas. One relevant GDB-related function is the formation of intentions to move, which is characterized by ramping activity of neural populations in SMA, followed by corresponding increases in neural activity in ACC (Fried et al., 2011). This may reflect the formation of motor execution plans or an attempt for ACC to integrate the information to the rest of the network. In either case, SMA damage may lead to reduced functioning in connected ACC neurons, which have been deprived of a direct input (diaschisis). Over time, poor axonal nutrient transport and mitochondrial dysfunction lead to the anterograde degeneration of axons (Coleman, 2005) in cingulate motor fibers and then within the ACC itself (transneuronal degeneration). In both cases, according to the model we propose here, apathy is the result.

The parietal-premotor network can be used as an example to consider how progressive damage to subnetworks might lead to apathy, as this has been implicated in a recent network study of the condition (Tay et al., 2019). This network consists primarily of the premotor and posterior parietal cortices, which form a relatively closed loop underlying movement intention and inhibition independently of motor execution (Desmurget and Sirigu, 2009). Partial damage

or disconnection of the structures within this loop, while not directly leading to apathy, may impair the synchronous timing of neural signals necessary for movement. This decreased network efficiency makes complex movements more difficult to execute, leading to perceived task-related effort costs appearing greater (Zénon et al., 2015), as the network needs to work harder (i.e., expend more energy) to achieve normal levels of functioning (Ginsberg et al., 1989). The result is postulated to lead to an overall decrease of GDB which might not be severe enough to meet criteria for an apathetic state. Over time, diaschisis and transneuronal degeneration occur within this network, leading to greater efficiency deficits that manifest as increasing apathy. The function of these structures and circuits has been simplified here for the purposes of illustrating how damage to non-hub nodes may lead to apathy. A more detailed discussion of the functional anatomy of these networks, and how damage to them may lead to apathy, can be found in Section 4.

The subsequent subsections will review evidence that suggests that apathy can be modeled as a network pathology in stroke (Section 3.3) and SVD (Section 3.4). Prior to this, however, we clarify the neuroanatomical terminology used in these sections, as well as the studies included in the scope of the discussion. Although GDB may have a firm basis in specific brain regions and connections, very few studies have examined apathy using this level of granularity. This may be a consequence of small sample sizes in most studies, which limits the number of patients with isolated infarcts in each area. Our description of research on a per-study basis will therefore reflect the terminology used by the authors as closely as possible, since extrapolation to more specific structures is not possible. Additionally, any research that assesses the relationship between apathy and stroke using very broad neuroanatomical

divisions (e.g., left/right hemisphere, anterior/posterior, etc.) will not be discussed, as these are too nonspecific to aid a mechanistic understanding of apathy.

3.3. Apathy in stroke

Apathy, in the acute and early subacute phase of stroke, may be the product of functional changes to nodes that are either part of or distant from the initial infarct. This is supported by a study of apathy and N-acetylaspartate (NAA) in first-time ischemic stroke patients (Glodzik-Sobanska et al., 2005). NAA is a nervous system-specific metabolite that may reflect myelin lipid turnover and mitochondrial energy production in humans, and can be interpreted as a marker for overall neuronal health (Moffett et al., 2007). Remarkably, the authors found that patients with apathy had reductions in prefrontal NAA levels despite all participants having lesions *outside* the frontal lobes, which was apparent an average of nine days post-stroke (Glodzik-Sobanska et al., 2005). In a similar vein, an electroencephalography study of patients with subcortical stroke showed that apathy was associated with decreased P3 amplitude and reduced P3 latency over frontal sites (Yamagata et al., 2004). The P3 is an event-related potential evoked by novel stimuli (Friedman et al., 2001), and the P3 changes documented by the authors may be consistent with decreased network efficiency in distant regions.

Studies of apathy and rCBF show converging results. rCBF is a measure of the brain's hemodynamic response, which is spatially and temporally coupled to changes in local field potentials elicited by synaptic activity (Shibasaki, 2008). As a result of this neurovascular coupling, a change in rCBF can be interpreted as a change in regional neural activity (Raichle

and Mintun, 2006). Apathy has been associated with reduced prefrontal rCBF in patients with subcortical stroke, as well as cerebellar and thalamic infarcts (Demirtas-Tatlidede et al., 2013; de Oliveira Lanna et al., 2012; Okada et al., 1997), suggesting functional changes in neural populations distant to the acute infarct. Moreover, apathetic patients showed lower rCBF in the basal ganglia compared to non-apathetic patients one month after stroke (Onoda et al., 2011). These functional changes may persist for several years, as demonstrated by a case study of a patient with severe apathy who showed aberrant functional connectivity, assessed using resting-state functional MRI, in ACC despite a lack of lesions in that area (Siegel et al., 2014). Functional connectivity deficits and apathy levels remained stable after three years (Siegel et al., 2014). These findings further support the notion that apathy may occur as a syndrome of functional diaschisis in patients with stroke. That said, more longitudinal research is required to examine whether functional changes really lead to apathy.

Structural changes may later follow these functional changes. One study, which assessed ischemic stroke patients during the subacute phase of stroke (10-28 days) and six months after the event, found that increasing apathy was associated with delayed atrophy in the posterior cingulate cortex (Matsuoka et al., 2015). This atrophy may be the product of anterograde transneuronal degeneration (Fornito et al., 2015), which can occur between 18-54 months post-stroke (Duering et al., 2015). This secondary neurodegeneration is studied primarily using diffusion tensor imaging (DTI), an MRI technique used to measure molecular diffusion in biological tissue. Due to the hindered nature of water diffusion in tissues with complex architecture, such as those with coherent myelin fiber orientations, DTI measures such as fractional anisotropy (FA) can be used to infer the microstructural properties of underlying

white matter (Basser and Pierpaoli, 1996). DTI data can also be used for tractography, which attempts to reconstruct three-dimensional white matter pathways through a continuous diffusion vector field (e.g., Mori et al., 1999).

Evidence to support transneuronal degeneration as a network mechanism underlying apathy comes from two case studies of post-stroke patients with apathy with left or right caudate lesions in addition to prefrontal damage (Jang et al., 2019; Jang and Kwon, 2018). Both studies used diffusion tractography to reconstruct white matter pathways emanating from the caudate nucleus of both hemispheres. In both cases, white matter tracts joining the caudate and prefrontal cortex could not be reconstructed from the lesioned caudate even in areas lacking a radiologically visible infarct. Furthermore, caudate-prefrontal connectivity profiles were also truncated in the non-lesioned caudate in the opposite hemisphere. This suggests that secondary neurodegeneration resulting in cortical disconnection was a factor underlying apathy in these patients. This is further evidenced by associations between apathy and lesions to the internal capsule (Starkstein et al., 1993; Tatemichi et al., 1992), as well as reduced FA in the genu of the corpus callosum, anterior corona radiata, and white matter of the inferior frontal gyrus (Yang, X.-y. Shang, et al., 2015).

These white matter changes are likely to have direct consequences on whole-brain network connectivity. One study that explored tractography-derived white matter networks in ischemic stroke patients showed that apathy was associated with decreased degree in 24 nodes across the cerebral cortex (Yang, Hua, et al., 2015). This included changes to the bilateral inferior frontal gyrus *pars orbitalis*, bilateral posterior cingulum, left SMA, and right putamen and thalamus. Other nodes correlated with apathy were found in the occipital, temporal, and

parietal lobes, as well as the insula. These changes in nodal degree were paralleled by decreased global and local efficiency in the nodes of the apathy-related subnetwork. Notably, DTI data was acquired within seven days of stroke onset, while assessments of apathy were conducted one month post-stroke. We can therefore conclude that early changes in the connectivity between these regions may predict the onset of apathy one month later. Whether these network changes result in apathy contemporaneously remains unexplored.

This is not to suggest that apathy, during the acute and post-acute phases of stroke, is *only* a product of diaschisis and transneuronal degeneration. Focal lesions to GDB-related hub nodes may lead to immediate network failure and apathy. For instance, apathy is a prominent feature of many patients with isolated ACC (Kumral et al., 2019), thalamic (Ghika-Schmid and Bogousslavsky, 2000), and striatal infarcts (Bhatia and Marsden, 1994). Similarly, reward sensitivity deficits, which are associated with apathy in chronic stroke patients, can be mapped to lesions in structures that include the ventral basal ganglia, thalamus, and PFC (Adam et al., 2013; Rochat et al., 2013). These demonstrate that hub node lesions can affect networks at large, without spreading to connected nodes.

These results suggest that post-stroke apathy can result from two different types of damage. One is driven by an acute lesion to a hub node, which causes immediate network failure and apathy. The other is driven by an acute lesion to a peripheral node, which, if connected to a hub node, can lead to a decrease in functioning of that hub node. Over time, these functional changes may lead to structural changes, such as cortical atrophy due to a loss of synaptic input. Our model therefore suggests that connectomal diaschisis, later followed by transneuronal degeneration, may be a mechanism underlying post-stroke apathy in cases

where the initial infarct occurs in a non-hub node. These connectivity changes could result in decreased global and local efficiency due to disconnection or disruption of the white matter networks underlying GDB.

This view of the pathogenesis of post-stroke apathy allows us to explain two major inconsistencies in the current literature. One is the lack of association between apathy and lesion location. As previously discussed, lesion location alone cannot adequately capture distant structural or functional changes that may lead to apathy. This may be why pairwise comparisons of lesion location in stroke patients with apathy against those without apathy yield negative results, while studies examining all patients with apathy find common structural and functional changes (e.g., Okada et al., 1997; Yang et al., 2015).

The second inconsistency concerns the trajectory of post-stroke apathy. Some patients without apathy in the acute phase develop it up to one year later, while some patients with apathy in the acute phase are apathy-free later (Caeiro, Ferro, Pinho e Melo, et al., 2013; Withall et al., 2011). Some of this may well be attributable to measurement error, as a diagnosis of apathy is usually made using cut scores on clinical scales. However, a potential neurobiological explanation for this crossover effect may be individual changes in functional network dynamics. In the former scenario, later-onset apathy may be the result of time-dependent post-stroke transneuronal degeneration, as previously described. Indeed, overall levels of apathy tend to increase in stroke patients over five years, although this may be due to subsequent cerebrovascular incidents (Brodaty et al., 2013).

In the latter case, remitting apathy may be the result of functional network reorganization, a notable phenomenon studied most extensively in the context of motor

recovery after stroke (Grefkes and Fink, 2014). This entails an initial disruption of functional network connectivity following stroke, which is then followed by a gradual restoration of interhemispheric functional connectivity over several months in individuals who recover function (van Meer et al., 2010). Evidence to support this functional network recovery in stroke patients with apathy comes from case studies using brain stimulation. Repetitive transcranial magnetic stimulation (rTMS) coils induce electrical fields that lead to the depolarization of superficial cortical axons, inducing activity in potentially disrupted networks (Lefaucheur et al., 2014). This form of stimulation, applied in certain cortical areas, may lead to a recovery of function over many sessions.

Such a recovery has been demonstrated in a sample of 13 chronic stroke patients who received high-frequency rTMS over the ACC and medial PFC, two putative hub nodes (Sasaki et al., 2017). After five days of treatment, individuals in the rTMS group showed an improvement in apathy symptoms. In contrast, apathy scores in individuals assigned to the sham condition remained static. That said, the five-day treatment regime used in this study is relatively short, and the final apathy assessment took place immediately after the final rTMS session. This makes it difficult to determine whether the improvements seen in this study reflect genuine functional network reorganization or transient network changes observed during or directly after high-frequency rTMS sessions (Sack, 2006).

A case study suggests that these rTMS-based decreases in post-stroke apathy are associated with improved interhemispheric activity (Mitaki et al., 2016), suggesting a direct parallel with the mechanisms underlying motor recovery after stroke. This functional network recovery may be the result of vicariation, when neighboring tissues take on functions related to

damaged tissue (Dancause, 2006). It has been suggested that structures that show similar connectivity profiles to the damaged tissues may be more likely to adopt these functions (Silasi and Murphy, 2014). Thus, an accurate understanding of the structural network basis of GDB may open up new targets for rTMS-based recovery in patients with post-stroke apathy.

3.4. Apathy in cerebral small vessel disease

Cerebral SVD is a term used to describe the pathologies that affect the small vessels of the brain, which include the small arteries, arterioles, and venules (Pantoni, 2010). SVD is the leading vascular cause of dementia (Pantoni, 2010). Most SVD is sporadic and related to age and vascular risk factors such as hypertension, but a minority of cases are caused by monogenic disorders, such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (Pantoni, 2010). SVD-related pathology is heterogenous and can manifest radiologically as lacunes, WMH, or microbleeds, among others (Wardlaw et al., 2013). These may occur in tandem with microstructural degeneration in major white matter tracts, leading to cognitive deficits that some have suggested to be the result of a disconnection syndrome (Lawrence et al., 2013; O'Sullivan et al., 2005).

Mounting evidence suggests that white matter damage may underlie apathy in SVD. Apathy has been associated with reduced FA in major white matter tracts such as the anterior cingulum and corpus callosum in patients with sporadic SVD (Hollocks et al., 2015) (Figure 2A). FA reductions in these same tracts were found to be associated with apathy in CADASIL (Le Heron, Manohar, et al., 2018) (Figure 2B), an early-onset model of SVD free of age-related neurodegeneration (Chabriat et al., 2009). In accordance with these changes, apathy has been

found to be associated with disruption to large-scale white matter networks in SVD (Tay et al., 2019) (Figure 2C).

FIGURE 2 AROUND HERE

Widespread white matter network damage is a known consequence of SVD (Tuladhar et al., 2019), although the etiology of this phenomenon remains incompletely understood. Research in this area largely focuses on understanding the pathophysiology underlying the radiological manifestations of SVD (Wardlaw et al., 2019). Apathy in particular has been associated with lacunar infarcts and WMH (Grool et al., 2014; Lavretsky et al., 2008; Sarabia-Cobo et al., 2014; Starkstein et al., 1997; Tay et al., 2019; Yao et al., 2009). We will now review the cerebrovascular pathologies that putatively underpin these markers of SVD and how they may lead to network damage.

Lacunar infarcts, while an important marker of SVD, have indirectly been covered in Section 3.3, as these tend to be sources of subcortical infarcts (Wardlaw et al., 2013). Although lacunes have different etiologies than large artery infarcts, which arise from the occlusion of larger cerebral arteries and often involve the cortex, both types of stroke tend to result in similar pathophysiological cascades, and thus similar patterns of network damage (Duering et al., 2015). The relationship between apathy and other radiological markers of SVD such as microbleeds, cortical microinfarcts, and enlarged perivascular spaces has yet to be explored.

WMH appear as areas of high signal intensity on T2-weighted MRI, and may reflect areas of ischemic demyelination and axonal loss resulting from chronic hypoperfusion (Fazekas et al., 1993; Fernando et al., 2006). These lead to changes in the underlying white matter architecture of the affected tissue and surrounding areas, corresponding to decreased FA and

NAA in proximal normal-appearing white matter (Firbank et al., 2003; van Leijsen, Bergkamp, et al., 2018). Tract-specific WMH progression is also related to incident cortical atrophy in the regions connected by that tract (Lambert et al., 2016). This suggests that WMH-related network damage can be characterized by transneuronal degeneration, which originates in hypoperfused white matter and progresses down tracts. This then leads to atrophy in connected regions due to the progressive disruption of synaptic inputs.

WMH have been correlated with higher apathy levels in population-based cohort studies (Grool et al., 2014; Yao et al., 2009), and Alzheimer's disease patients with WMH have higher levels of apathy compared to patients without WMH (Starkstein et al., 1997). These are paralleled by lower rCBF in basal ganglia, thalamus, and frontal lobes (Starkstein et al., 1997), suggesting that WMH lead to functional disruption of GDB-related hub nodes, which may impact network efficiency. This notion is supported by a study of SVD patients that showed that global white matter network efficiency fully mediated the relationship between WMH volumes and apathy (Tay et al., 2019). Although these results are cross-sectional, they suggest that WMH are related to apathy through the disruption of network efficiency. This, coupled with progressive neurodegeneration and consequent cortical thinning, may be a factor underlying apathy in SVD. The consequences of this chronic ischemia, together with the earlier mentioned effect of acute infarcts, suggests a potential cascade linking ischemia to apathy (Figure 3).

FIGURE 3 AROUND HERE

4. Neurocognitive mechanisms underlying apathy

If damage to distinct networks leads to the behavioral symptoms of apathy, then they may do so through defined neurocognitive mechanisms. For the purposes of this review, we will consider apathy to be a deficit in the cognitive processes underlying effort-based decision making due to the conceptual simplicity and operationalizability of this approach (Le Heron, Apps, et al., 2018; Le Heron et al., 2019). This view suggests that behavior can be thought of in three distinct phases:

1. Deciding whether to pursue a behavior;
2. Performing and persisting with the behavior; and
3. Evaluating and learning the costs and benefits of a behavior.

4.1. Reward-based decision-making

Prior to any behavior occurring, an individual must decide whether or not that behavior is worth engaging in. This engages networks that underlie cost-benefit valuation, as rewards and effort costs must be appraised. Apathy may therefore be the result of reductions in reward sensitivity, which is typically operationalized as an tendency to respond in proportion to the value of a rewarding stimulus during a behavioral task.

Recent evidence suggests that reduced incentivization to rewards may be a mechanism underlying apathy in cerebrovascular disease. Decreased reward-related task speeding is associated with apathy in chronic stroke patients (Rochat et al., 2013). Similarly, CADASIL patients with apathy rejected more opportunities to exert effort during a task, and were slower in making effort-related decisions, when compared to patients without apathy (Le Heron,

Manohar, et al., 2018). This was paralleled by reduced FA in the anterior cingulum, white matter of the OFC, and the anterior internal capsule (Le Heron, Apps, et al., 2018). Rejection of opportunities to exert effort suggests that apathy in these patients reflects a devaluation of rewards, while the increased decision-making time and concurrent white matter damage may reflect disrupted network efficiency. This is directly supported by a study of white matter subnetworks in sporadic SVD patients, which showed that the global efficiency of a reward-related subnetwork was more correlated with apathy than motor or visual subnetworks (Lisiecka-Ford et al., 2018). The reward-related subnetwork included nodes such as ACC, OFC, and putamen (including ventral striatum), among others (Lisiecka-Ford et al., 2018). Changes in the connectivity between these frontostriatal structures was associated with apathy in an independent cohort of sporadic SVD patients (Tay et al., 2019).

This collective evidence suggests a direct pathway between cerebrovascular pathology, network change, cognitive deficits, and apathy. First, neuropathological changes lead to frontostriatal network damage, either through cortical or subcortical infarcts that lead to secondary neurodegenerative cascades down white matter tracts (Duering et al., 2015; Schaapsmeerders et al., 2016), or through frontal WMH, which represent areas of ischemic demyelination and axonal loss (Gouw et al., 2011). Both infarcts and WMH may also lead to incident cortical atrophy in connected regions (Duering et al., 2015; Lambert et al., 2016). The progressive destruction or disruption of these frontal white matter tracts may lead to a decrease in the efficiency of information transfer along these tracts, making the integration of reward-related signals between structures such as ACC, ventral striatum, and PFC (Haber and Knutson, 2010) more difficult. In turn, these can lead to a decrease in the perceived rewarding

value of a stimulus, manifesting as a reduction in GDB and apathy. These deficits in reward sensitivity may well be synonymous with the 'affective blunting' described in accounts of apathy related to impaired emotional processing (Levy and Dubois, 2006).

These changes may be modulated by dopaminergic neurons, which originate in the ventral tegmental area and substantia nigra and project to the ventral striatum, ACC, ventromedial PFC, and OFC (Chong and Husain, 2016). Dopamine may promote approach behaviors by attributing incentive salience to rewarding stimuli (Chong and Husain, 2016). Accordingly, case studies show that the administration of dopamine agonists can alleviate apathy in some stroke patients. These include bromocriptine (Barrett, 1991; Catsman-Berrevoets and Harskamp, 1988; Marin et al., 1995; Parks et al., 1992; Powell et al., 1996), and ropinirole (Adam et al., 2013; Kohno et al., 2010).

Changes in dopaminergic neurotransmission may explain associations between apathy and inflammation (Chen et al., 2018; Eurelings et al., 2015). Systemic inflammation can be estimated by circulating plasma C-reactive protein (CRP) levels, which are elevated following an inflammatory response (Pepys and Baltz, 1983). Elevated acute phase CRP levels are associated with increasing post-stroke apathy over six months (Chen et al., 2018). Similarly, apathy was correlated with higher CRP levels over several years in community-dwelling individuals (Eurelings et al., 2015). This relationship may be driven by inflammation-associated decreases in dopamine synthesis and availability, reducing neural responses toward rewarding stimuli (Felger and Treadway, 2017). It should be noted, however, that inflammation itself is related to incident vascular disease (Gounis et al., 2015), meaning that the relationship between inflammatory markers and apathy may additionally be mediated by other factors such as WMH

(Yao et al., 2019). Clearly dissociating the direct and indirect effects of inflammation on apathy is an important topic for future research.

4.2. Attentional control during behavior

After a behavior is initiated, it must be sustained until completion to achieve the desired outcome. This involves not only monitoring current outcomes of a task, but also comparing the potential value of completing the current task to others which are potentially more rewarding. If this is the case, then it possible that patients with apathy may also show deficits in cognitive flexibility.

There is some indirect evidence to support this hypothesis. Apathy is associated with worse performance on composite cognitive indices that include the Trail Making Test Part B (TMT-B) (Reitan, 1958) in stroke and SVD (Douven et al., 2018; Lohner et al., 2017). TMT-B performance requires individuals to draw a line between alternating numbers and letters in consecutive order, and completion requires the maintenance of a long sequence of behaviors as well as the ability to switch between two contexts (numbers and letters) (Kortte et al., 2002). The reduction in TMT-B performance may reflect patient difficulties in completing a long sequence of behaviors, switching between rewarding contexts, or switching to more rewarding options. The latter two, while difficult to dissociate using current data on the TMT-B, may reflect difficulties in sustaining motivation through a task.

These associations, however, are indirect, as TMT-B performance in both studies was included in a larger composite index that included other measures of executive functioning (Douven et al., 2018; Lohner et al., 2017). Although these composite cognitive indices are

robust and easy to interpret, variance in the measures used to construct them may obfuscate true associations. For instance, another study that measured executive function using the TMT-B found no correlation between executive function and apathy scores (Brodaty et al., 2005). This may be due to that executive function index including a color-form sorting task, which may assess different cognitive abilities than TMT-B (Tamkin and Kunce, 1982). The inclusion of both, therefore, may have dampened associations with apathy. More direct testing of these constructs, as well as careful consideration towards tests used to create composite cognitive indices, is required before any definitive conclusions can be drawn.

The deficits discussed above may be associated with impairment of the fronto-parietal and cingulo-opercular networks, two intrinsic connectivity networks derived from resting-state functional MRI data (Seeley et al., 2007). The fronto-parietal network includes the dorsolateral PFC, inferior parietal lobule, intraparietal sulcus, precuneus, and middle cingulate, while the cingulo-opercular network includes anterior PFC, anterior insula, dorsal ACC, and thalamus (Seeley et al., 2007). Both networks have been implicated in attentional control processes, with fronto-parietal network initiating and adjusting behavior on a task-to-task basis, while the cingulo-opercular network provides stable maintenance of task goals over the entire behavioral period (Dosenbach et al., 2008).

Apathy in SVD patients is associated with altered connectivity in white matter networks that have a similar topological organization to these intrinsic connectivity networks (Tay et al., 2019). Furthermore, after controlling for general cognitive functioning, which included measures of attention, apathy was no longer associated with these particular white matter networks (Tay et al., 2019). Although no direct analysis of resting-state functional connectivity

was conducted, structural connectivity has been shown to constrain functional connectivity in the human brain (Honey et al., 2009). Therefore, structural damage to the nodes or edges supporting the fronto-parietal and cingulo-opercular networks may result in attentional deficits. These make the maintenance of task-related GDB more difficult, manifesting as apathy. It should be noted that all current evidence that supports this notion is indirect, highlighting the need for more focused, theory-driven network analyses of apathy.

4.3. Learning and remembering rewarding behaviors

After a behavior has been completed, outcomes reveal whether the behavior was a success or failure. The magnitude of the success or failure, in relation to the effort exerted to complete the task, informs individuals of how worthwhile the task was. Deficits in learning this action-outcome contingency may impair individuals from learning rewarding behaviors, which may manifest as apathy (Husain and Roiser, 2018).

Evidence, in general, supports an association between apathy and impaired measures of verbal recall and recognition in stroke and SVD (Brodaty et al., 2005; Fishman et al., 2018a; Lohner et al., 2017), although some studies do not find this association (Douven et al., 2018). In accordance with this, apathy has been found to be associated with reduced FA in the fornix, the major output tract of the hippocampus, in sporadic SVD (Hollocks et al., 2015), as well as with reduced nodal degree in left hippocampus in ischemic stroke patients (Yang, Hua, et al., 2015). That said, apathy has not been found to be associated with hippocampal connectivity in a less severe cohort of SVD patients (Tay et al., 2019), and apathy is not associated with reduced fornix FA in patients with CADASIL or all-cause ischemic stroke (Le Heron, Manohar, et al., 2018;

Yang, X.-y. Shang, et al., 2015). Apathy is also not generally associated with altered medial temporal lobe connectivity in stroke or SVD, despite lateral temporal lobe differences being found (Tay et al., 2019; Yang, Hua, et al., 2015).

Apathy has also been documented as a comorbidity with amnesia following thalamic stroke (Carrera and Bogousslavsky, 2006; Catsman-Berrevoets and Harskamp, 1988; Guberman and Stuss, 1983). This may be due to the reciprocal connections between the thalamus and the hippocampus via the mammillo-thalamic tract, which includes the fornix (Carlesimo et al., 2011). Interpreting this is not straightforward, however, as disrupted white matter connectivity between the thalamus and PFC may also underlie apathy (Tay et al., 2019). Future research could clarify whether thalamic-hippocampal connectivity plays a role in learning and memory deficits associated with apathy by examining tract-specific white matter microstructure in patients with vascular thalamic amnesia and apathy.

The evidence to support a link between cerebrovascular disease, medial temporal network damage, learning and memory deficits, and apathy therefore remains inconclusive. These associations may be further complicated by depression and Alzheimer's disease pathology in elderly patients, both of which are associated with medial temporal lobe changes that may interact with cerebrovascular pathology to produce age-related changes in learning and memory (Geerlings et al., 2008; van Leijsen, Tay, et al., 2018). More focused behavioral experiments, together with more rigorous sample population phenotyping, may be able to better clarify these relationships.

Aside from the medial temporal lobes, damage to structures such as the ACC and VS may also impair the learning of rewarding behaviors given their established roles in appetitive

conditioning (Parkinson et al., 2000). Dopaminergic neurons within VS provide a key substrate for reward prediction error signals (Pagnoni et al., 2002), which in turn are used by ACC to update internal models of the environment and task (Kolling et al., 2016). Damage to these structures may therefore lead to learning deficits which lead to improper value signaling, thereby leading to inaccurate reward-based decisions (e.g. Section 4.1).

Links between these components of GDB, underlying cognitive functions, and potential subnetworks that may support these are shown in Figure 4. It is important to note that the way we have presented these is, overall, a simplified view of how neurobiological networks might be related to apathetic behaviors. It is unlikely that one single subnetwork or connection underlies a specific behavior or cognition, as this is quite contrary to the notion of networks in general. For instance, attention must be sustained throughout all phases of behavior, as a lack of attention may impair decision-making and learning. Instead, we have highlighted specific cognitive functions that may be particularly important to a certain phase of behavior, and have related that to properties of established functional networks that may be disrupted in cerebrovascular disease. Interactions between these networks, which could be mediated by GDB-related hub nodes, may well play a role in determining multiple components of behavior.

FIGURE 4 AROUND HERE

5. Apathy as a predisposing factor for vascular disease

The relationship between apathy and cerebrovascular disease raises an interesting question regarding causality. On one hand, apathy could be the result of cerebrovascular damage to brain networks underlying GDB. On the other hand, apathy could reduce GDB that

are important for mitigating vascular risk factors, which could then cause cerebrovascular disease. Although the latter scenario is not related to mechanisms linking cerebrovascular disease to apathy *per se*, reverse causality is an important methodological consideration for future studies investigating apathy, and therefore merits some discussion. As a result, we will briefly discuss evidence that shows that apathy can be a predisposing factor for incident vascular disease, as well as the relationships between apathy and specific vascular risk factors.

Large, community-based cohort studies have found that apathy is associated with higher rates of cardiovascular diseases other than stroke, such as myocardial infarction, angina pectoris, or peripheral artery disease (Ligthart et al., 2012; Van der Mast et al., 2008). Furthermore, apathy is an independent risk factor for incident cardiovascular disease after two-year follow-up, even after adjustment for demographic factors, cardiovascular risk factors, cognition, and disability (Eurelings et al., 2014). This implies that apathy is associated with increased vascular burden, which is borne out by data from a large cohort study showing that apathy is associated with increased vascular risk factors such as elevated systolic blood pressure, high body mass index (BMI), and type 2 diabetes mellitus (Ligthart et al., 2012). A follow-up study in the same cohort suggested that the relationships between apathy and incident vascular disease was primarily mediated by physical inactivity, along with diabetes and smoking (Eurelings et al., 2016). Associations between apathy and physical inactivity have been reported in other populations (Yao et al., 2015).

Apathy may also lead to vascular disease through diabetes mellitus. In a large sample of community-dwelling individuals, diabetes was shown to partially mediate the relationship between apathy and incident vascular disease (Eurelings et al., 2016). Furthermore, patients

with diabetes have higher apathy compared to healthy controls (Bruce et al., 2015). This raises the possibility that apathy may be a contributory factor leading to diabetes, which in turn leads to vascular disease. This relationship may be attributed to apathy causing diabetic patients to be less adherent to exercise plans or insulin regimes, which is reflected in slightly elevated levels of glycated hemoglobin (HbA1c) in apathetic diabetes patients compared to diabetics without apathy (Padala et al., 2008).

These lines of evidence imply that apathy may play a role in incident vascular disease. Subthreshold levels of apathy in healthy individuals are associated with individual differences in structural and functional connectivity in ACC and SMA (Bonnelle et al., 2015), important areas underlying apathy (see Sections 3.2 and 4).

Given this evidence, it is tempting to speculate that a higher body mass index (BMI) should be one of the manifestations of apathy, given its association with exercise. However, apathy has been associated with *lower* BMI and weight loss in patients with pre-existing neurological diseases (Rodríguez-Violante et al., 2014; Sobów et al., 2014; Volicer et al., 2013). Apathy in outpatients with Alzheimer's disease has actually been associated with nutritive deficits (Benoit et al., 2008), suggesting that apathetic patients may be less inclined to eat. This may lead to a deficiency in dietary vitamins such as vitamin B6, B12, and folate, which can lead to elevated homocysteine levels and subsequent strokes (He et al., 2004; Larsson et al., 2019).

It is therefore possible that apathy may lead to incident vascular disease through two pathways. One is through individual differences in network structural and functional connectivity in GDB-related regions, leading to individuals who do not adequately manage their vascular risk factors, such as physical exercise. Another may be in individuals who already have

pre-existing diseases, such as Alzheimer's, where patients may not engage in important behaviors related to self-maintenance, such as eating. The reciprocal relationships between apathy and vascular disease can be found in Figure 5.

FIGURE 5 AROUND HERE

6. Model predictions and future directions

The network-based view of apathy that we have proposed, along with the potential cognitive mechanisms that may link network damage to apathy, provide a fruitful basis for future hypotheses. Our model can be tested on multiple levels, including: the specific cerebrovascular pathologies that lead to network damage in stroke and SVD (Section 3), the neurocognitive processes proposed to support motivated behavior, and the anatomical and functional specificity of the subnetworks that may support these processes (Section 4). Some testable and falsifiable questions that arise from a network-based model of apathy are highlighted in Box 1.

BOX 1 AROUND HERE

Validation of the specific hub nodes and subnetworks underlying apathy in stroke and SVD (Tay et al., 2019; Yang, Hua, et al., 2015) may lead to a better understanding of the structural and functional connections and subnetworks that are impaired in individuals with specific cerebrovascular pathologies. These pathologies may include the under-explored areas of post-stroke neuroinflammation or the ischemic penumbra, which may play roles in exacerbating or alleviating apathy. Moreover, a clearer understanding of specific subnetwork connectivity related to GDB could lead to *a priori* investigations using networks of interest (e.g.,

Lisiecka-Ford et al., 2018). These subnetworks could also be examined in the context of other comorbidities, such as depression and fatigue (Douven, Köhler, Schievink, et al., 2017), in order to identify common underlying mechanisms.

Studies on the trajectories of post-stroke apathy could investigate whether functional diaschisis underlies apathy in the acute phase. Longitudinal research could examine whether patients who recovery from apathy show corresponding improvements in intrahemispheric connectivity or vicariation, and if individuals who develop apathy show transneuronal degeneration in connected cortical regions. These network pathologies should help explain why apathy develops after lesions in certain areas.

Further inquiry into the validity of the presented neurocognitive framework for apathy is needed, as well as the subnetworks that support these cognitive functions. This could involve behavioral paradigms or cognitive tests that assess specific constructs that may be related to apathy, with additional consideration to any comorbidities that a patient might show. Doing so may identify which components of GDB are disrupted in patients with cerebrovascular disease. Additionally, work on how some cognitive mechanisms may be related to multiple phases of GDB is needed, as this evidence is largely absent.

It is possible that many of these questions could also be evaluated in animal models. Although apathy *per se* is not traditionally investigated in animal studies, several components of GDB, such as option generation, action initiation, and learning have been investigated in rodent models (see Husain and Roiser, 2018). This work could be extended by new studies that use experimental stroke models such as photothrombosis and endothelin-1 to model circumscribed and reproducible brain lesions (Sommer, 2017). This approach might be applied to specific brain

regions to determine whether disruption to the proposed hub nodes and subnetworks leads to the distinct neurocognitive deficits that may underlie apathy (Section 3.2 and 4).

All of these lines of research could lead to targeted interventions for treating apathy. For instance, an apathetic patient with damage in a defined apathy-related subnetwork might be treated with rTMS, which requires *a priori* knowledge of which nodes may be disrupted. Such rTMS approaches have some preliminary support (Mitaki et al., 2016; Sasaki et al., 2017). Alternatively, subnetwork-specific neurotransmitter deficits could be addressed with pharmacological agents, such as dopamine agonists, which lead to a reinstatement of the related component of GDB (Adam et al., 2013). Treating apathy may not only lead to improvements in patient functional outcomes, but also lower the risk of future vascular disease.

Cerebrovascular pathology also plays an important part in neurodegenerative conditions such as Alzheimer's disease (Korczyn, 2002), which could potentially lead to more severe apathy. For instance, Alzheimer's disease patients with WMH have higher levels of apathy compared to Alzheimer's patients without WMH (Starkstein et al., 1997). Given these findings, it is possible that understanding apathy in cerebrovascular disease could lead to potential mechanistic insights and treatment approaches into apathy in other neurological conditions.

These findings also suggest that our network-based model of apathy may be extensible and generalizable to other conditions. For instance, different neurodegenerative diseases target distinct large-scale networks (Seeley et al., 2009), making it reasonable to assume that disease-specific patterns of network damage could lead to different symptoms of apathy. Modeling apathy as the result of network pathology could lead to a better understanding of the nature of

motivational impairments in specific diseases, which could assist in clinical phenotyping. Findings could then be integrated across diseases to identify core networks underlying GDB.

Finally, future research should also focus on verifying the proposed pathways linking apathy to incident vascular disease (Section 5). The preliminary evidence we have presented suggests that apathy in otherwise neurologically healthy individuals may lead to incident vascular disease, although further replication with more detailed measures of apathy is required. If these relationships are verified, then addressing subthreshold levels of apathy in the general population may lead to an overall reduction in vascular burden, which has important implications for public health (Baumgart et al., 2015).

7. Conclusion

Apathy is a complex phenomenon that cannot be fully explained by current lesion-based theories. To address this, we have proposed a network-based model of apathy that connects cerebrovascular disease - both focal lesions, such as ischemic and hemorrhagic stroke, and widespread white matter disruption, such as in SVD - to observed neurobiological changes. The evidence reviewed suggests that network pathologies, particularly diaschisis and transneuronal degeneration, can be used to explain how apathy may present in individuals without direct GDB-related hub node damage. These pathologies may also be able to explain improving or worsening trajectories of apathy over time. Our consideration of the literature suggests potential cognitive mechanisms underlying GDB, as well as how specific subnetworks may support them.

Conceptualizing of apathy as the result of large-scale network pathologies may open new pathways for investigating its neurobiology, clinical presentation, and longitudinal trajectory. Validation of the cognitive components of apathy, as well as the specific subnetworks that support these, may help in understanding the specific GDB-related networks that are affected in patients with cerebrovascular disease. This has the potential to lead to novel diagnostic tools and targeted treatment approaches for this prevalent and debilitating condition.

Funding

This work is funded by a Priority Programme Grant from the Stroke Association (PPA 2015-02) and National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) Dementia and Neurodegeneration Theme (146281). JT is supported by a Cambridge International Scholarship from the Cambridge Trust. AMT has received a grant from the Junior Staff Member Dutch Heart Foundation (2016T044). F-EdL has received the Innovational Research Incentive grant (ZonMW 016-126-351) and the Clinical established investigator Dutch Heart Foundation grant (2014T060). MH is supported by a Wellcome Trust Principal Research Fellowship (098282) and the NIHR Oxford BRC. HSM is supported by an NIHR Senior Investigator Award. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Box 1. Network model predictions.

A network-based framework of apathy leads to several potential lines of inquiry. These can be broadly categorized into three inter-related domains, namely, the cerebrovascular pathologies that lead to apathy-related network damage, the neurocognitive mechanisms that may underlie apathy, and the specific subnetworks supporting these neurocognitive functions. These yield testable and falsifiable questions, such as:

1. **Cerebrovascular pathologies**
   - Do circumscribed strokes in hub nodes lead to acute apathy?
   - Do strokes in peripheral nodes lead to increasing apathy over time?
   - Is increasing apathy associated with connectomal diaschisis or transneuronal degeneration?
   - Can these network pathologies be mapped to stereotyped pathophysiological cascades after stroke, such as anterograde (Wallerian) degeneration?
2. **Neurocognitive mechanisms**
   - Can different presentations of apathy be associated with deficits in the neurocognitive domains described?
   - Do apathetic patients show difficulties in making rewarding decisions?
   - Do apathetic patients show difficulties in switching between rewarding contexts?
   - Do apathetic patients show difficulties in learning rewarding behaviors?
3. **Subnetwork functioning**
   - Do specific subnetworks correspond to the abovementioned neurocognitive processes (e.g., does damage to the ACC-insula-orbitofrontal-VS subnetwork lead to reward sensitivity deficits?)
   - Do previously identified structural subnetworks (e.g., Tay et al., 2019; Yang et al., 2015) include all relevant nodes and connections?
   - Can the function of specific subnetworks be mapped to discernable neural processes (e.g., is learning subnetwork function associated with aberrant reward prediction error signalling?)

References

Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., Husain, M., 2013. Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. Cortex 49, 1292–1303.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed. Author, Washington, DC.

Bandyopadhyay, T.K., Biswas, A., Roy, A., Guin, D.S., Gangopadhyay, G., Sarkhel, S., Ghoshal, M.K., Senapati, A.K., 2014. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. Ann Indian Acad Neurol 17, 325–330.

Baron, J., Rougemont, D., Soussaline, F., Bustany, P., Crouzel, C., Bousser, M., Comar, D., 1984. Local interrelationships of cerebral oxygen consumption and glucose utilization in normal subjects and in ischemic stroke patients: A positron tomography study. J Cereb Blood Flow Metab 4, 140–149.

Barrett, K., 1991. Treating organic abulia with bromocriptine and lisuride: Four case studies. J Neurol Neurosur Psychiatry 54, 718–721.

Basser, P.J., Pierpaoli, C., 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111, 209–219.

Bassett, D.S., Bullmore, E.T., Meyer-Lindenberg, A., Apud, J.A., Weinberger, D.R., Coppola, R., 2009. Cognitive fitness of cost-efficient brain functional networks. Proc Natl Acad Sci 106, 11747–11752.

Baumgart, M., Snyder, H.M., Carrillo, M.C., Fazio, S., Kim, H., Johns, H., 2015. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement 11, 718–726.

Benoit, M., Andrieu, S., Lechowski, L., Gillette-Guyonnet, S., Robert, P., Vellas, B., 2008. Apathy and depression in Alzheimer's disease are associated with functional deficit and psychotropic prescription. Int J Geriatr Psychiatry 23, 409–414.

Bhatia, K.P., Marsden, C.D., 1994. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117, 859–876.

Bonnelle, V., Manohar, S., Behrens, T., Husain, M., 2015. Individual differences in premotor brain systems underlie behavioral apathy. Cereb Cortex 26, 807–819.

Brodaty, H., Liu, Z., Withall, A., Sachdev, P.S., 2013. The longitudinal course of post-stroke apathy over five years. J Neuropsychiatry Clin Neurosci 25, 283–291.

Brodaty, H., Sachdev, P.S., Withall, A., Altendorf, A., Valenzuela, M.J., Lorentz, L., 2005. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke–the Sydney Stroke Study. Psychol Med 35, 1707–1716.

Bruce, D.G., Nelson, M.E., Mace, J.L., Davis, W.A., Davis, T.M., Starkstein, S.E., 2015. Apathy in older patients with type 2 diabetes. Am J Geriatr Psychiatry 23, 615–621.

Bullmore, E., Sporns, O., 2009. Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10, 186–198.

Caeiro, L., Ferro, J.M., Costa, J., 2013. Apathy secondary to stroke: A systematic review and meta-analysis. Cerebrovasc Dis 35, 23–39.

Caeiro, L., Ferro, J.M., Pinho e Melo, T., Canhão, P., Figueira, M.L., 2013. Post-stroke apathy: An exploratory longitudinal study. Cerebrovasc Dis 35, 507–513.

Carlesimo, G.A., Lombardi, M.G., Caltagirone, C., 2011. Vascular thalamic amnesia: A reappraisal. Neuropsychologia 49, 777–789.

Carrera, E., Bogousslavsky, J., 2006. The thalamus and behavior: Effects of anatomically distinct strokes. Neurology 66, 1817–1823.

Carrera, E., Tononi, G., 2014. Diaschisis: Past, present, future. Brain 137, 2408–2422.

Catsman-Berrevoets, C.E., Harskamp, F., 1988. Compulsive pre-sleep behavior and apathy due to bilateral thalamic stroke: Response to bromocriptine. Neurology 38, 647–649.

Chabriat, H., Joutel, A., Dichgans, M., Tournier-Lasserve, E., Bousser, M.-G., 2009. CADASIL. Lancet Neurol 8, 643–653.

Chen, L., Xiong, S., Liu, Y., Lin, M., Wang, J., Zhong, R., Zhao, J., Liu, W., Zhu, L., Shang, X., 2018. C-reactive protein can be an early predictor of poststroke apathy in acute ischemic stroke patients. J Stroke Cerebrovasc Dis 27, 1861–1869.

Chong, T.-J., Husain, M., 2016. The role of dopamine in the pathophysiology and treatment of apathy, in: Progress in Brain Research. Elsevier, pp. 389–426.

Coleman, M., 2005. Axon degeneration mechanisms: Commonality amid diversity. Nat Rev Neurosci 6, 889–898.

Collin, G., Sporns, O., Mandl, R.C., van den Heuvel, M.P., 2013. Structural and functional aspects relating to cost and benefit of rich club organization in the human cerebral cortex. Cereb Cortex 24, 2258–2267.

Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: The seven pillars of rdoc. BMC Med 11, 126.

Dancause, N., 2006. Vicarious function of remote cortex following stroke: Recent evidence from human and animal studies. Neuroscientist 12, 489–499.

Demirtas-Tatlidede, A., Bahar, S.Z., Gurvit, H., 2013. Akinetic mutism without a structural prefrontal lesion. Cogn Behav Neurol 26, 59–62.

de Oliveira Lanna, M.E., Alves, C.E.O., Sudo, F.K., Alves, G., Valente, L., Moreira, D.M., Cavalcanti, J.L.S., Engelhardt, E., 2012. Cognitive disconnective syndrome by single strategic strokes in vascular dementia. J Neurol Sci 322, 176–183.

de Reus, M.A., van den Heuvel, M.P., 2013. The parcellation-based connectome: Limitations and extensions. Neuroimage 80, 397–404.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., others, 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.

Desmurget, M., Sirigu, A., 2009. A parietal-premotor network for movement intention and motor awareness. Trends Cogn Sci 13, 411–419.

Dosenbach, N.U., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cogn Sci 12, 99–105.

Douven, E., Köhler, S., Rodriguez, M.M., Staals, J., Verhey, F.R., Aalten, P., 2017. Imaging markers of post-stroke depression and apathy: A systematic review and meta-analysis. Neuropsychol Rev 27, 202–219.

Douven, E., Köhler, S., Schievink, S.H., van Oostenbrugge, R.J., Staals, J., Verhey, F.R., Aalten, P., 2018. Baseline vascular cognitive impairment predicts the course of apathetic symptoms after stroke: The CASPER study. Am J Geriatr Psychiatry 26, 291–300.

Douven, E., Köhler, S., Schievink, S.H., van Oostenbrugge, R.J., Staals, J., Verhey, F.R., Aalten, P., 2017. Temporal associations between fatigue, depression, and apathy after stroke: Results of the cognition and affect after stroke, a prospective evaluation of risks study. Cerebrovasc Dis 44, 330–337.

Duering, M., Righart, R., Wollenweber, F.A., Zietemann, V., Gesierich, B., Dichgans, M., 2015. Acute infarcts cause focal thinning in remote cortex via degeneration of connecting fiber tracts. Neurology 84, 1685–1692.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25, 1325–1335.

Eurelings, L.S., Jaccard, J., Moll van Charante, E.P., Eikelenboom, P., Ligthart, S.A., van Gool, W.A., Richard, E., 2016. The mediating role of cardiovascular risk factors in the relationship between symptoms of apathy and incident cardiovascular disease in community-dwelling older individuals. Int Psychogeriatr 28, 669–679.

Eurelings, L.S., Ligthart, S.A., van Dalen, J.W., Moll van Charante, E.P., van Gool, W.A., Richard, E., 2014. Apathy is an independent risk factor for incident cardiovascular disease in the older individual: A population-based cohort study. Int J Geriatr Psychiatry 29, 454–463.

Eurelings, L.S., Richard, E., Eikelenboom, P., van Gool, W.A., Moll van Charante, E.P., 2015. Low-grade inflammation differentiates between symptoms of apathy and depression in community-dwelling older individuals. Int Psychogeriatr 27, 639–647.

Eurelings, L.S., van Dalen, J.W., ter Riet, G., Moll van Charante, E.P., Richard, E., van Gool, W.A., ICARA Study Group, others, 2018. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: A systematic review and meta-analysis of individual participant data. Clin Epidemiol 10, 363–379.

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., Radner, H., Lechner, H., 1993. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 43, 1683–1689.

Felger, J.C., Treadway, M.T., 2017. Inflammation effects on motivation and motor activity: Role of dopamine. Neuropsychopharmacology 42, 216–241.

Fernando, M.S., Simpson, J.E., Matthews, F., Brayne, C., Lewis, C.E., Barber, R., Kalaria, R.N., Forster, G., Esteves, F., Wharton, S.B., others, 2006. White matter lesions in an unselected cohort of the elderly: Molecular pathology suggests origin from chronic hypoperfusion injury. Stroke 37, 1391–1398.

Firbank, M., Minett, T., O'Brien, J., 2003. Changes in DWI and MRS associated with white matter hyperintensities in elderly subjects. Neurology 61, 950–954.

Fishman, K.N., Ashbaugh, A.R., Lanctôt, K.L., Cayley, M.L., Herrmann, N., Murray, B.J., Sicard, M., Lien, K., Sahlas, D.J., Swartz, R.H., 2018a. The role of apathy and depression on verbal learning and memory performance after stroke. Arch Clin Neuropsychol 34, 327–336.

Fishman, K.N., Ashbaugh, A.R., Lanctôt, K.L., Cayley, M.L., Herrmann, N., Murray, B.J., Sicard, M., Lien, K., Sahlas, D.J., Swartz, R.H., 2018b. Apathy, not depressive symptoms, as a predictor of semantic and phonemic fluency task performance in stroke and transient ischemic attack. J Clin Exp Neuropsychol 40, 449–461.

Fornito, A., Zalesky, A., Breakspear, M., 2015. The connectomics of brain disorders. Nat Rev Neurosci 16, 159–172.

Fried, I., Mukamel, R., Kreiman, G., 2011. Internally generated preactivation of single neurons in human medial frontal cortex predicts volition. Neuron 69, 548–562.

Friedman, D., Cycowicz, Y.M., Gaeta, H., 2001. The novelty P3: An event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neurosci Biobehav Rev 25, 355–373.

Fuh, J., Wang, S., Cummings, J., 2005. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. J Neurol Neurosur Psychiatry 76, 1337–1341.

Geerlings, M., den Heijer, T., Koudstaal, P.J., Hofman, A., Breteler, M., 2008. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology 70, 1258–1264.

Ghika-Schmid, F., Bogousslavsky, J., 2000. The acute behavioral syndrome of anterior thalamic infarction: A prospective study of 12 cases. Ann Neurol 48, 220–227.

Ginsberg, M.D., Castella, Y., Dietrich, W.D., Watson, B.D., Busto, R., 1989. Acute thrombotic infarction suppresses metabolic activation of ipsilateral somatosensory cortex: Evidence for functional diaschisis. J Cereb Blood Flow Metab 9, 329–341.

Glodzik-Sobanska, L., Slowik, A., Kieltyka, A., Kozub, J., Sobiecka, B., Urbanik, A., Szczudlik, A., 2005. Reduced prefrontal N-acetylaspartate in stroke patients with apathy. J Neurol Sci 238, 19–24.

Gounis, M.J., Marel, K. van der, Marosfoi, M., Mazzanti, M.L., Clarençon, F., Chueh, J.-Y., Puri, A.S., Bogdanov Jr, A.A., 2015. Imaging inflammation in cerebrovascular disease. Stroke 46, 2991–2997.

Gouw, A.A., Seewann, A., Van Der Flier, W.M., Barkhof, F., Rozemuller, A.M., Scheltens, P., Geurts, J.J., 2011. Heterogeneity of small vessel disease: A systematic review of MRI and histopathology correlations. J Neurol Neurosur Psychiatry 82, 126–135.

Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol 13, 206–216.

Grool, A.M., Geerlings, M.I., Sigurdsson, S., Eiriksdottir, G., Jonsson, P.V., Garcia, M.E., Siggeirsdottir, K., Harris, T.B., Sigmundsson, T., Gudnason, V., others, 2014. Structural MRI correlates of apathy symptoms in older persons without dementia: AGES-Reykjavik Study. Neurology 82, 1628–1635.

Guberman, A., Stuss, D., 1983. The syndrome of bilateral paramedian thalamic infarction. Neurology 33, 540–546.

Haber, S.N., Knutson, B., 2010. The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.

Hama, S., Yamashita, H., Shigenobu, M., Watanabe, A., Hiramoto, K., Kurisu, K., Yamawaki, S., Kitaoka, T., 2007. Depression or apathy and functional recovery after stroke. Int J Geriatr Psychiatry 22, 1046–1051.

Hargrave, R., Geck, L.C., Reed, B., Mungas, D., 2000. Affective behavioural disturbances in Alzheimer's disease and ischaemic vascular disease. J Neurol Neurosur Psychiatry 68, 41–46.

He, K., Merchant, A., Rimm, E.B., Rosner, B.A., Stampfer, M.J., Willett, W.C., Ascherio, A., 2004. Folate, vitamin B6, and B12 intakes in relation to risk of stroke among men. Stroke 35, 169–174.

Hollocks, M.J., Lawrence, A.J., Brookes, R.L., Barrick, T.R., Morris, R.G., Husain, M., Markus, H.S., 2015. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. Brain 138, 3803–3815.

Honey, C., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.-P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci 106, 2035–2040.

Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: A transdiagnostic approach. Nat Rev Neurosci 19, 470–484.

Iadecola, C., 2010. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Acta Neuropathol 120, 287–296.

Jang, S.H., Kim, S.H., Kwon, H.G., 2019. Injury of the prefronto-caudate tract in a patient with apathy following intracerebral hemorrhage in the caudate nucleus. Acta Neurol Belg 119, 143–145.

Jang, S.H., Kwon, Y.H., 2018. Abulia due to injury of the prefrontocaudate tract in a stroke patient. Am J Phys Med Rehabil 97, e76–e77.

Kohno, N., Abe, S., Toyoda, G., Oguro, H., Bokura, H., Yamaguchi, S., 2010. Successful treatment of post-stroke apathy by the dopamine receptor agonist ropinirole. J Clin Neurosci 17, 804–806.

Kolling, N., Wittmann, M.K., Behrens, T.E., Boorman, E.D., Mars, R.B., Rushworth, M.F., 2016. Value, search, persistence and model updating in anterior cingulate cortex. Nat Neurosci 19, 1280–1285.

Korczyn, A.D., 2002. Mixed dementia—the most common cause of dementia. Ann NY Acad Sci 977, 129–134.

Kortte, K.B., Horner, M.D., Windham, W.K., 2002. The trail making test, part B: Cognitive flexibility or ability to maintain set? Appl Neuropsychol 9, 106–109.

Kos, C., van Tol, M.-J., Marsman, J.-B.C., Knegtering, H., Aleman, A., 2016. Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and psychiatric disorders. Neurosci Biobehav Rev 69, 381–401.

Kumral, E., Erdoğan, C.E., Bayam, F.E., Arslan, H., 2019. Cingulate infarction: A neuropsychological and neuroimaging study. J Neurol Sci 402, 1–6.

Lambert, C., Benjamin, P., Zeestraten, E., Lawrence, A.J., Barrick, T.R., Markus, H.S., 2016. Longitudinal patterns of leukoaraiosis and brain atrophy in symptomatic small vessel disease. Brain 139, 1136–1151.

Lanctôt, K.L., Agüera-Ortiz, L., Brodaty, H., Francis, P.T., Geda, Y.E., Ismail, Z., Marshall, G.A., Mortby, M.E., Onyike, C.U., Padala, P.R., others, 2017. Apathy associated with neurocognitive disorders: Recent progress and future directions. Alzheimers Dement 13, 84–100.

Larsson, S.C., Traylor, M., Markus, H.S., 2019. Homocysteine and small vessel stroke: A mendelian randomization analysis. Ann Neurol 85, 495–501.

Latora, V., Marchiori, M., 2001. Efficient behavior of small-world networks. Phys Rev Lett 87, 198701.

Lavretsky, H., Zheng, L., Weiner, M.W., Mungas, D., Reed, B., Kramer, J.H., Jagust, W., Chui, H., Mack, W.J., 2008. The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. Int J Geriatr Psychiatry 23, 1040–1050.

Lawrence, A.J., Patel, B., Morris, R.G., MacKinnon, A.D., Rich, P.M., Barrick, T.R., Markus, H.S., 2013. Mechanisms of cognitive impairment in cerebral small vessel disease: Multimodal MRI results from the St George's cognition and neuroimaging in stroke (SCANS) study. PLoS One 8, e61014.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., others, 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125, 2150–2206.

Le Heron, C., Apps, M., Husain, M., 2018. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia 118, 54–67.

Le Heron, C., Holroyd, C.B., Salamone, J., Husain, M., 2019. Brain mechanisms underlying apathy. J Neurol Neurosur Psychiatry 90, 302–312.

Le Heron, C., Manohar, S., Plant, O., Muhammed, K., Griffanti, L., Nemeth, A., Douaud, G., Markus, H.S., Husain, M., 2018. Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. Brain 141, 3193–3210.

Levy, R., Dubois, B., 2006. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. Cereb Cortex 16, 916–928.

Ligthart, S.A., Richard, E., Fransen, N.L., Eurelings, L.S., Beem, L., Eikelenboom, P., van Gool, W.A., Moll van Charante, E.P., 2012. Association of vascular factors with apathy in community-dwelling elderly individuals. Arch Gen Psychiatry 69, 636–642.

Lisiecka-Ford, D.M., Tozer, D.J., Morris, R.G., Lawrence, A.J., Barrick, T.R., Markus, H.S., 2018. Involvement of the reward network is associated with apathy in cerebral small vessel disease. J Affect Disord 232, 116–121.

Lohner, V., Brookes, R.L., Hollocks, M.J., Morris, R.G., Markus, H.S., 2017. Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. PLoS One 12, e0176943.

Marin, R.S., 1991. Apathy: A neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3, 243–254.

Marin, R.S., Fogel, B.S., Hawkins, J., Duffy, J., Krupp, B., 1995. Apathy: A treatable syndrome. J Neuropsychiatry Clin Neurosci 7, 23–30.

Matsuoka, K., Yasuno, F., Taguchi, A., Yamamoto, A., Kajimoto, K., Kazui, H., Kudo, T., Sekiyama, A., Kitamura, S., Kiuchi, K., others, 2015. Delayed atrophy in posterior cingulate cortex and apathy after stroke. Int J Geriatr Psychiatry 30, 566–572.

Matsuzaki, S., Hashimoto, M., Yuki, S., Koyama, A., Hirata, Y., Ikeda, M., 2015. The relationship between post-stroke depression and physical recovery. J Affect Disord 176, 56–60.

Mayo, N.E., Fellows, L.K., Scott, S.C., Cameron, J., Wood-Dauphinee, S., 2009. A longitudinal view of apathy and its impact after stroke. Stroke 40, 3299–3307.

Mitaki, S., Onoda, K., Abe, S., Oguro, H., Yamaguchi, S., 2016. The effectiveness of repetitive transcranial magnetic stimulation for poststroke apathy is associated with improved interhemispheric functional connectivity. J Stroke Cerebrovasc Dis 25, e219–e221.

Moffett, J.R., Ross, B., Arun, P., Madhavarao, C.N., Namboodiri, A.M., 2007. N-acetylaspartate in the CNS: From neurodiagnostics to neurobiology. Prog Neurobiol 81, 89–131.

Mori, S., Crain, B.J., Chacko, V.P., Van Zijl, P.C., 1999. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45, 265–269.

Nachev, P., Kennard, C., Husain, M., 2008. Functional role of the supplementary and pre-supplementary motor areas. Nat Rev Neurosci 9, 856–869.

Oguru, M., Tachibana, H., Toda, K., Okuda, B., Oka, N., 2010. Apathy and depression in parkinson disease. J Geriatr Psychiatry Neurol 23, 35–41.

Okada, K., Kobayashi, S., Yamagata, S., Takahashi, K., Yamaguchi, S., 1997. Poststroke apathy and regional cerebral blood flow. Stroke 28, 2437–2441.

Onoda, K., Kuroda, Y., Yamamoto, Y., Abe, S., Oguro, H., Nagai, A., Bokura, H., Yamaguchi, S., 2011. Post-stroke apathy and hypoperfusion in basal ganglia: SPECT study. Cerebrovasc Dis 31, 6–11.

O'Sullivan, M., Barrick, T., Morris, R., Clark, C., Markus, H., 2005. Damage within a network of white matter regions underlies executive dysfunction in CADASIL. Neurology 65, 1584–1590.

Padala, P.R., Desouza, C.V., Almeida, S., Shivaswamy, V., Ariyarathna, K., Rouse, L., Burke, W.J., Petty, F., 2008. The impact of apathy on glycemic control in diabetes: A cross-sectional study. Diabetes Res Clin Pract 79, 37–41.

Pagnoni, G., Zink, C.F., Montague, P.R., Berns, G.S., 2002. Activity in human ventral striatum locked to errors of reward prediction. Nat Neurosci 5, 97–98.

Pagonabarraga, J., Kulisevsky, J., Strafella, A.P., Krack, P., 2015. Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol 14, 518–531.

Pantoni, L., 2010. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 9, 689–701.

Parkinson, J.A., Cardinal, R.N., Everitt, B.J., 2000. Limbic cortical-ventral striatal systems underlying appetitive conditioning, in: Progress in Brain Research. Elsevier, pp. 263–285.

Parks, R., Crockett, D., Manji, H., Ammann, W., 1992. Assessment of bromocriptine intervention for the treatment of frontal lobe syndrome: A case study. J Neuropsychiatry Clin Neurosci 4, 109–111.

Pepys, M.B., Baltz, M.L., 1983. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein, in: Advances in Immunology. Elsevier, pp. 141–212.

Powell, J.H., Al-Adawi, S., Morgan, J., Greenwood, R.J., 1996. Motivational deficits after brain injury: Effects of bromocriptine in 11 patients. J Neurol Neurosur Psychiatry 60, 416–421.

Radakovic, R., Harley, C., Abrahams, S., Starr, J.M., 2015. A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions. Int Psychogeriatr 27, 903–923.

Raichle, M.E., Mintun, M.A., 2006. Brain work and brain imaging. Annu Rev Neurosci 29, 449–476.

Reitan, R.M., 1958. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills 8, 271–276.

Reyes, S., Viswanathan, A., Godin, O., Dufouil, C., Benisty, S., Hernandez, K., Kurtz, A., Jouvent, E., O'Sullivan, M., Czernecki, V., others, 2009. Apathy: A major symptom in CADASIL. Neurology 72, 905–910.

Robert, P., Lanctôt, K., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., Hanon, C., David, R., Dubois, B., Dujardin, K., others, 2018. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry 54, 71–76.

Rochat, L., Van der Linden, M., Renaud, O., Epiney, J.-B., Michel, P., Sztajzel, R., Spierer, L., Annoni, J.-M., 2013. Poor reward sensitivity and apathy after stroke: Implication of basal ganglia. Neurology 81, 1674–1680.

Rodríguez-Violante, M., González-Latapi, P., Cervantes-Arriaga, A., Martínez-Ramírez, D., Velázquez-Osuna, S., Camacho-Ordoñez, A., 2014. Apathy and associated factors in Mexican patients with Parkinson's disease. Neurol Sci 35, 729–734.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: Uses and interpretations. Neuroimage 52, 1059–1069.

Sack, A.T., 2006. Transcranial magnetic stimulation, causal structure–function mapping and networks of functional relevance. Curr Opinion Neurobiol 16, 593–599.

Sagnier, S., Munsch, F., Bigourdan, A., Debruxelles, S., Poli, M., Renou, P., Olindo, S., Rouanet, F., Dousset, V., Tourdias, T., others, 2019. The influence of stroke location on cognitive and mood impairment. A voxel-based lesion-symptom mapping study. J Stroke Cerebrovasc Dis 28, 1236–1242.

Sarabia-Cobo, C.M., Pérez, V., Hermosilla, C., Nuñez, M.J., de Lorena, P., 2014. Apathy and leukoaraiosis in mild cognitive impairment and Alzheimer's disease: Multicenter diagnostic criteria according to the latest studies. Dement Geriatr Cogn Disord Extra 4, 228–235.

Sasaki, N., Hara, T., Yamada, N., Niimi, M., Kakuda, W., Abo, M., 2017. The efficacy of high-frequency repetitive transcranial magnetic stimulation for improving apathy in chronic stroke patients. Eur Neurol 78, 28–32.

Schaapsmeerders, P., Tuladhar, A.M., Arntz, R.M., Franssen, S., Maaijwee, N.A., Rutten-Jacobs, L.C., Schoonderwaldt, H.C., Dorresteijn, L.D., Dijk, E.J. van, Kessels, R.P., others, 2016. Remote lower white matter integrity increases the risk of long-term cognitive impairment after ischemic stroke in young adults. Stroke 47, 2517–2525.

Schindlbeck, K.A., Eidelberg, D., 2018. Network imaging biomarkers: Insights and clinical applications in Parkinson's disease. Lancet Neurol 17, 629–640.

Schroeter, M.S., Charlesworth, P., Kitzbichler, M.G., Paulsen, O., Bullmore, E.T., 2015. Emergence of rich-club topology and coordinated dynamics in development of hippocampal functional networks in vitro. J Neurosci 35, 5459–5470.

Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D., 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron 62, 42–52.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27, 2349–2356.

Shibasaki, H., 2008. Human brain mapping: Hemodynamic response and electrophysiology. Clin Neurophysiol 119, 731–743.

Siegel, J., Snyder, A., Metcalf, N., Fucetola, R., Hacker, C., Shimony, J., Shulman, G., Corbetta, M., 2014. The circuitry of abulia: Insights from functional connectivity MRI. Neuroimage Clin 6, 320–326.

Silasi, G., Murphy, T.H., 2014. Stroke and the connectome: How connectivity guides therapeutic intervention. Neuron 83, 1354–1368.

Sobów, T., Fendler, W., Magierski, R., 2014. Body mass index and mild cognitive impairment-to-dementia progression in 24 months: A prospective study. Eur J Clin Nutr 68, 1216–1219.

Sommer, C.J., 2017. Ischemic stroke: Experimental models and reality. Acta Neuropathol 133, 245–261.

Starkstein, S.E., Fedoroff, J.P., Price, T.R., Leiguarda, R., Robinson, R.G., 1993. Apathy following cerebrovascular lesions. Stroke 24, 1625–1630.

Starkstein, S.E., Ingram, L., Garau, M., Mizrahi, R., 2005. On the overlap between apathy and depression in dementia. J Neurol Neurosur Psychiatry 76, 1070–1074.

Starkstein, S.E., Manes, F., 2000. Apathy and depression following stroke. Cns Spectr 5, 43–50.

Starkstein, S.E., Sabe, L., Vazquez, S., Di Lorenzo, G., Martinez, A., Petracca, G., Teson, A., Chemerinski, E., Leiguarda, R., 1997. Neuropsychological, psychiatric, and cerebral perfusion correlates of leukoaraiosis in alzheimer's disease. J Neurol Neurosur Psychiatry 63, 66–73.

Tamkin, A.S., Kunce, J.T., 1982. Construct validity of the Weigl Color-Form Sorting Test. Percept Mot Skills 55, 105–106.

Tang, W., Chen, Y., Liang, H., Chu, W.C., Mok, V., Ungvari, G.S., Wong, K., 2013. Location of infarcts and apathy in ischemic stroke. Cerebrovasc Dis 35, 566–571.

Tatemichi, T., Desmond, D., Cross, D., Gropen, T., Mohr, J., 1992. Confusion and memory loss from capsular genu infarction: A thalamocortical disconnection syndrome? Neurology 42, 1966–1979.

Tay, J., Tuladhar, A.M., Hollocks, M.J., Brookes, R.L., Tozer, D.J., Barrick, T.R., Husain, M., de Leeuw, F.-E., Markus, H.S., 2019. Apathy is associated with large-scale white matter network disruption in small vessel disease. Neurology 92, e1157–e1167.

Tuladhar, A.M., Tay, J., van Leijsen, E.M., Lawrence, A.J., van Uden, I.W.M., Bergkamp, M.I., van der Holst, E., Kessels, R.P., Norris, D., Markus, H.S., others, 2019. Structural network changes in cerebral small vessel disease. J Neurol Neurosur Psychiatry.

van Dalen, J.W., Moll van Charante, E.P., Nederkoorn, P.J., van Gool, W.A., Richard, E., 2013. Poststroke apathy. Stroke 44, 851–860.

van Dalen, J.W., van Wanrooij, L.L., Moll van Charante, E.P., Brayne, C., van Gool, W.A., Richard, E., 2018. Association of apathy with risk of incident dementia: A systematic review and meta-analysis. JAMA Psychiatry 75, 1012–1021.

van den Heuvel, M.P., Sporns, O., 2013. Network hubs in the human brain. Trends Cogn Sci 17, 683–696.

Van der Mast, R., Vinkers, D., Stek, M., Bek, M., Westendorp, R., Gussekloo, J., De Craen, A., 2008. Vascular disease and apathy in old age. The Leiden 85-plus study. Int J Geriatr Psychiatry 23, 266–271.

van Leijsen, E.M., Bergkamp, M.I., Van Uden, I.W., Ghafoorian, M., Van Der Holst, H.M., Norris, D.G., Platel, B., Tuladhar, A.M., de Leeuw, F.-E., 2018. Progression of white matter

hyperintensities preceded by heterogeneous decline of microstructural integrity. Stroke 49, 1386–1393.

van Leijsen, E.M., Tay, J., van Uden, I.W., Kooijmans, E.C., Bergkamp, M.I., dvan der Holst, H.M., Ghafoorian, M., Platel, B., Norris, D.G., Kessels, R.P., others, 2018. Memory decline in elderly with cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy. Hippocampus 29, 500–510.

van Meer, M.P., van der Marel, K., Wang, K., Otte, W.M., el Bouazati, S., Roeling, T.A., Viergever, M.A., van der Sprenkel, J.W.B., Dijkhuizen, R.M., 2010. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. J Neurosci 30, 3964–3972.

Vergani, F., Lacerda, L., Martino, J., Attems, J., Morris, C., Mitchell, P., de Schotten, M.T., Dell'Acqua, F., 2014. White matter connections of the supplementary motor area in humans. J Neurol Neurosurg Psychiatry 85, 1377–1385.

Volicer, L., Frijters, D.H., van der Steen, J.T., 2013. Apathy and weight loss in nursing home residents: Longitudinal study. J Am Med Dir Assoc 14, 417–420.

Wardlaw, J.M., Smith, C., Dichgans, M., 2019. Small vessel disease: Mechanisms and clinical implications. Lancet Neurol 18, 684–696.

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., others, 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12, 822–838.

Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of “small-world” networks. Nature 393, 440–442.

Withall, A., Brodaty, H., Altendorf, A., Sachdev, P.S., 2011. A longitudinal study examining the independence of apathy and depression after stroke: The Sydney Stroke Study. Int Psychogeriatr 23, 264–273.

Yamagata, S., Yamaguchi, S., Kobayashi, S., 2004. Impaired novelty processing in apathy after subcortical stroke. Stroke 35, 1935–1940.

Yang, S.-r., Hua, P., Shang, X., Cui, Z., Zhong, S., Gong, G., William Humphreys, G., 2015. Deficiency of brain structural sub-network underlying post-ischaemic stroke apathy. Eur J Neurol 22, 341–347.

Yang, S.-r., Shang, X.-y., Tao, J., Liu, J.-y., Hua, P., 2015. Voxel-based analysis of fractional anisotropy in post-stroke apathy. PLoS One 10, e116168.

Yao, H., Mizoguchi, Y., Monji, A., Yakushiji, Y., Takashima, Y., Uchino, A., Yuzuriha, T., Hashimoto, M., 2019. Low-grade inflammation is associated with apathy indirectly via deep white matter lesions in community-dwelling older adults: The Sefuri Study. Int J Mol Sci 20, 1905.

Yao, H., Takashima, Y., Araki, Y., Uchino, A., Yuzuriha, T., Hashimoto, M., 2015. Leisure-time physical inactivity associated with vascular depression or apathy in community-dwelling elderly subjects: The Sefuri study. J Stroke Cerebrovasc Dis 24, 2625–2631.

Yao, H., Takashima, Y., Mori, T., Uchino, A., Hashimoto, M., Yuzuriha, T., Miwa, Y., Sasaguri, T., 2009. Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: The Sefuri brain MRI study. Hypertens Res 32, 586–590.

Zénon, A., Sidibé, M., Olivier, E., 2015. Disrupting the supplementary motor area makes physical effort appear less effortful. J Neurosci 35, 8737–8744.

Figure legends

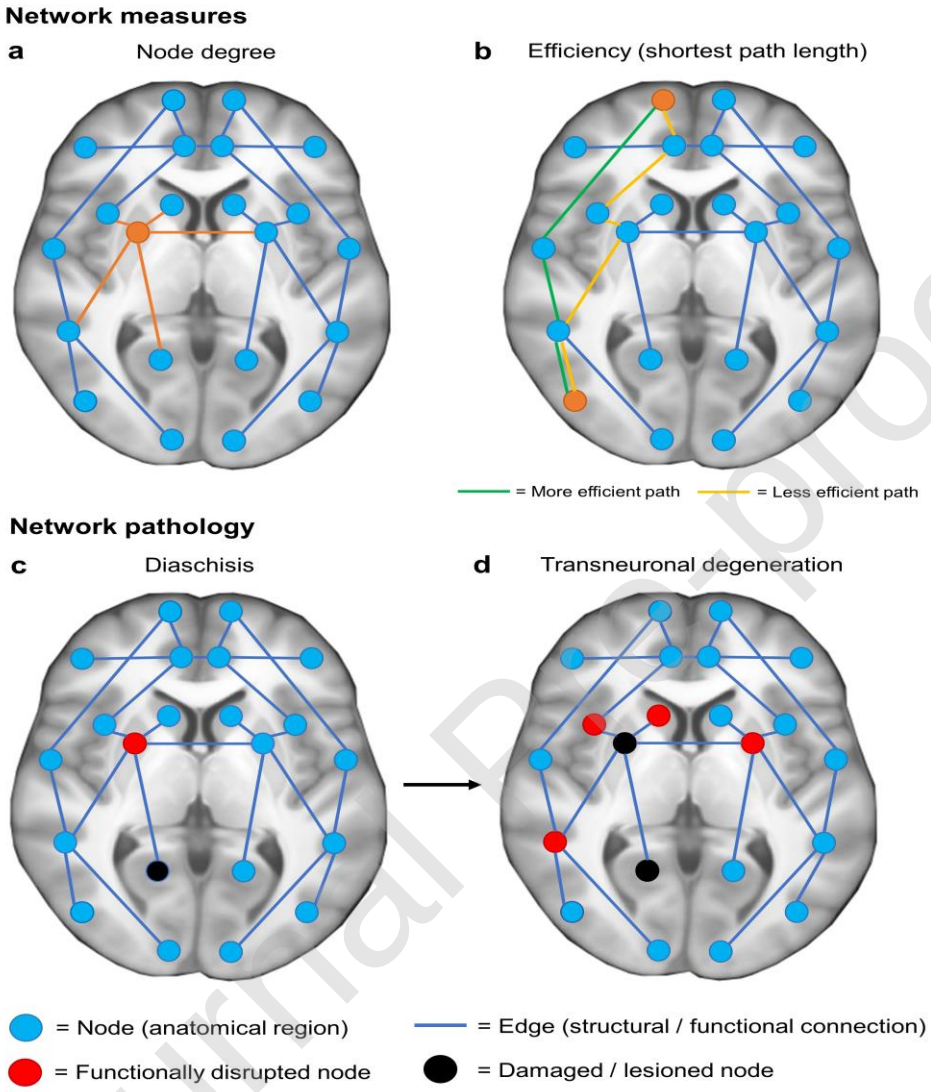

Figure 1. Basic network measures and pathology. **a,** The degree of a node is a measure of how many connections it has. **b,** The shortest path between two nodes is a measure of efficiency. **c,** Diaschisis is a functional deficit in a region that is remote from a damaged node; **d,** Transneuronal degeneration involves the physical breakdown of nodes, which propagates from connections to already damaged nodes.

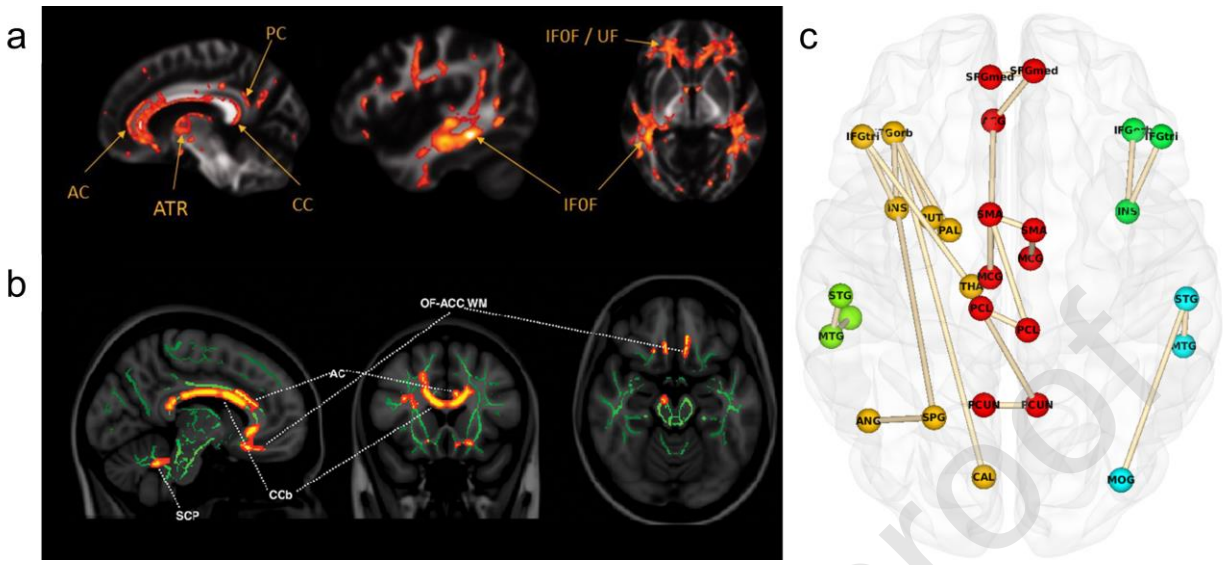

Figure 2. White matter network damage associated with apathy in cerebral small vessel disease (SVD). **a,** Apathy is associated with reduced white matter fractional anisotropy (FA) in patients with sporadic SVD. Red = FA voxels associated with apathy. **b,** CADASIL patients with apathy show reduced FA compared to CADASIL patients without apathy. Red = areas of reduced FA in apathetic CADASIL patients, green = white matter skeleton. **c,** Reductions in white matter network connectivity associated with apathy in sporadic SVD. Apathy is associated with a distributed pattern of white matter damage across the cortex, implicating several subnetworks in the pathogenesis of apathy. White matter damage related to apathy is consistent in sporadic and genetic SVD, suggesting a common basis. Adapted from Hollocks et al. (2015), Le Heron, Manohar, et al. (2018), and Tay et al. (2019) with permission. AC = anterior cingulum; PC = posterior cingulum; CC = corpus callosum; CCb = body of the corpus callosum; ATR = anterior thalamic radiation; IFOF = inferior fronto-occipital fasciculus; UF = uncinate fasciculus; SCP = superior cerebellar peduncle; OF-ACC WM = orbitofrontal-anterior cingulate cortex white matter.

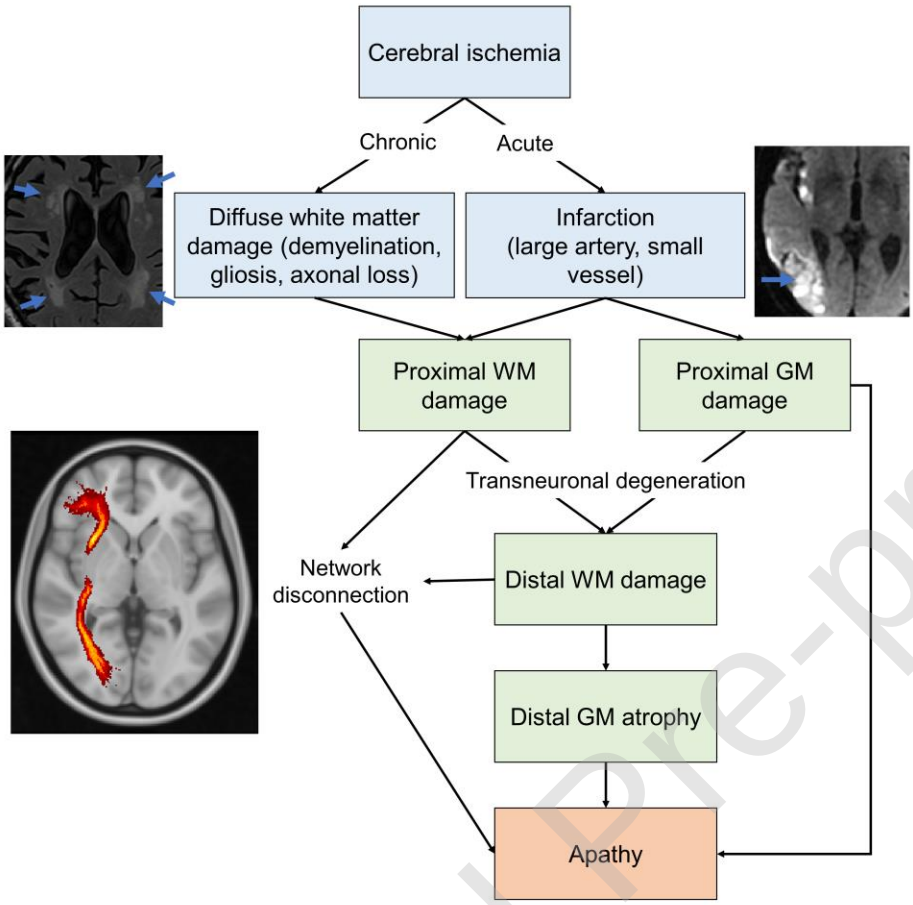

Figure 3. Hypothesized mechanisms linking ischemic pathology to apathy. Chronic and acute ischemia may lead to different types of tissue damage. Specific types of lesions that lead to damage in strategic grey matter structures or white matter tracts, such as those related to hub nodes, may immediately lead to apathy. Over time, secondary neurodegeneration propagates from lesioned tissue to connected areas, leading to network disconnection and apathy. GM = grey matter; WM = white matter.

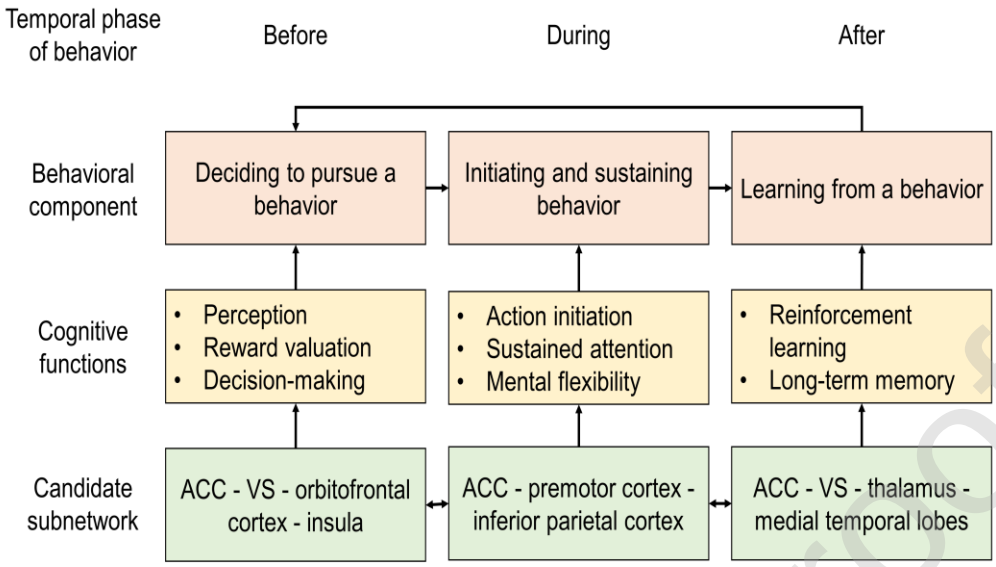

Figure 4. Potential relationships between subnetworks, cognition, and components of goal-directed behavior. Behavior may be thought of in three temporal phases: before, during, and after. Prior to behavior occurring, individuals must evaluate whether a behavior is worth engaging in. After a decision has been made, the behavior must be initiated and sustained. Once the behavior has been completed, the outcome of the behavior influences future decision-making. These may be supported by specific subnetworks implicated in incentive salience, executive control, and learning and memory. Some nodes may be part of multiple subnetworks, such as the anterior cingulate cortex (ACC) and ventral striatum (VS), as these may be hub nodes for goal-directed behavior. For simplicity, only one subnetwork has been listed per phase of behavior, though it should be noted that multiple subnetworks with more nodes than the ones listed may be involved.

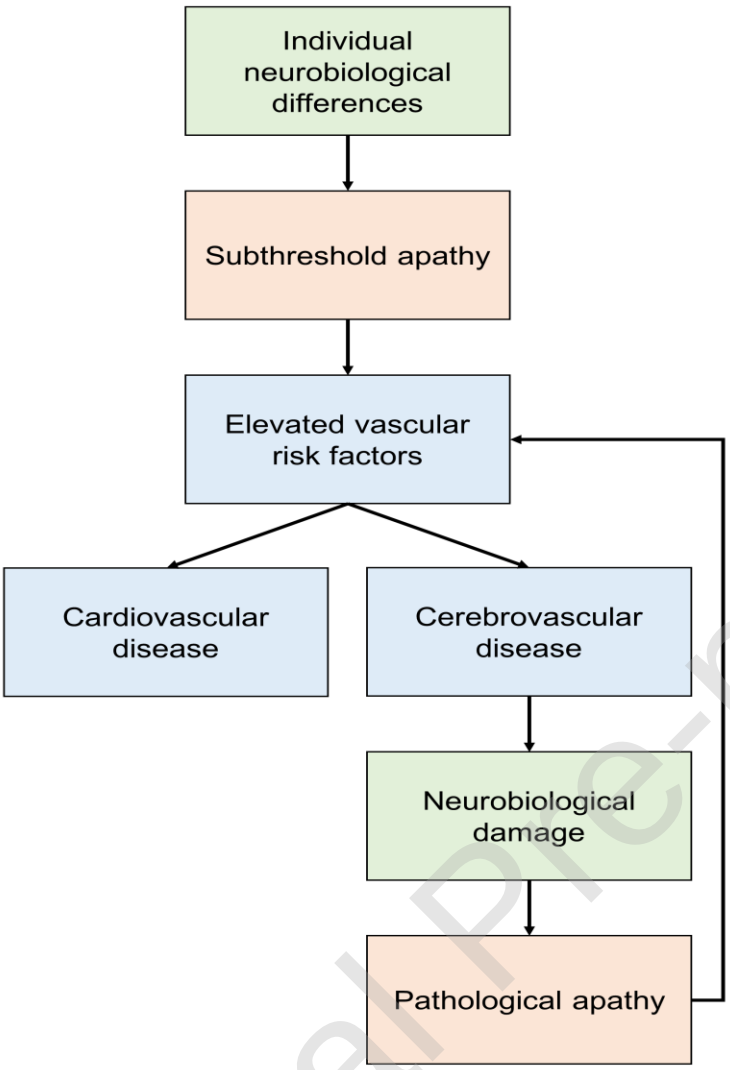

Figure 5. Pathways linking apathy to vascular disease. Individual differences in network functioning may lead to lower motivation in some individuals, This may lead to elevated risk factors such as physical inactivity, which may cause incident cardio- and cerebrovascular disease. Cerebrovascular pathology can exacerbate network damage and apathy, which has further consequences for managing vascular risk factors.