



Towards a Tensegrity Model of Mental Health

John Gardiner

Independent Researcher

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Australia

jgardiner88@bigpond.com

Abstract

The neuronal cytoskeleton can be seen as a tensegrity network. Microtubules are compression-resistant components and actin filaments tension-resistant components. Alzheimer's disease sees this healthy network compressed by extracellular amyloid plaques. This leads to collapse of the microtubule/actin tensegrity system and thus dementia. Parkinson's and epilepsy may be similar in some respects to Alzheimer's. Depression is seen in Alzheimer's disease and numerous other neuropathies. This is due to destruction of prestress in the cytoskeletal networks. In Hereditary Spastic Paraplegia microtubules are pathologically stabilised, which can lead to schizophrenia due to too much stress in the cytoskeletal network. Treatments which use the body's own tensegrity mechanisms including massage, posture, meditation and social contact are likely to be broadly useful.

Keywords: Act in filaments, Alzheimer's disease, Amyloid, Cytoskeleton, Depression, Meditation, Microtubules, Parkinson's, Schizophrenia, Tau protein, Tensegrity

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This work was created on Cammeraygal land. I acknowledge the continuing connection to land, water and sky of First Nations and that sovereignty has never been ceded. I pay respect to Elders past, present and future.

Cytoskeletal Tensegrity

Tensegrity is a term coined by R. Buckminster Fuller, originally as a mathematical construct (Fuller 1961). It relates to systems of interconnected compression-resistant and tension-resistant members under prestress. Kenneth Snelson co-discovered the concept in his artistic oeuvre. The Harvard biologist Donald Ingber saw that tensegrity could be applied to studies of cells' cytoskeletons, that microtubules are compression-resistant members strung together by tension-resistant

actin filaments (Ingber 2003). Subsequent experiments have confirmed this point of view. In previous papers I have argued that the brain is a tensegrity-dependent organ. Moreover I suggest that depression is a condition whereby there is not enough prestress in the brain's cytoskeletal networks and schizophrenia is a condition whereby there is too much. Below I elaborate on this using recent thinking.

Microtubules and Neurology

Recent work shows that acetylation of α -tubulin in microtubules is defective in a number of neurological disorders. This acetylation is the only known posttranslational modification of tubulin known to occur in the microtubule lumen. It is important for motor proteins to transit along



microtubules and enables microtubules to withstand bending, which contributes to their stability. Elongator protein complex, which is involved in Rolandic epilepsy, familial dysautonomia and amyotrophic lateral sclerosis amongst others, indirectly regulates tubulin acetylation (Shilian et al. 2022). Other neurological disorders including Huntington's disease and Charcot-Marie-Tooth disease (of which there are several types) show defects in microtubule acetylation and microtubule-based transport. Meaning microtubules are not as stable as they should be. Inhibition of the α -tubulin deacetylase HDAC6 in models of Charcot-Marie-Tooth disease restores microtubule-based transport, suggesting this as a potential therapeutic strategy (d'Ydewalle et al. 2011).

Alzheimer's is associated with increased tubulin acetylation (Martinez-Haernandez 2022), which may appear to confound this theory. But this is not necessarily so. At relatively low, localised pressures, microtubules are stabilised in living cells (Li et al. 2022). At extreme hydrostatic pressures they disintegrate (Gao et al. 2018). In Alzheimer's neurons are filled with neurofibrillary tangles of hyperphosphorylated Tau protein, linked to extracellular amyloid plaques via transmembrane β -amyloid precursor protein. As amyloid fibrils fail under low tensile loading (Paparcone 2010) this suggests they are compression-resistant. Tau proteins can "rupture" under compressive loading and refold in company into an "entangled" state, a possible mechanism for the formation of Tau aggregates (Chowdhury and Lu 2019). Extracellular compressive force from growing amyloid plaques may speed this process. Neurodegenerative neurons 'round up' and retract their processes (Joyce et al. 2011) and increasing hydrostatic pressure within plaque-surrounded neurons will eventually lead to cell death.

Another angle is that amyloid can form pentagonal forms, similar in shape to quasicrystalline neurotransmitter receptor complexes (Pinteric and Painter 1979). This

may enable them to bind neurotransmitter receptors, disrupting signalling. Indeed amyloid binds nicotinic $\alpha 7$ acetylcholine receptors at the synapse (Lasala et al 2019) and can activate the receptors (Dineley et al. 2002). These particular neurotransmitter receptors are important for microtubule dynamics in the growth cone (Nordman and Kabbani 2014), destabilising microtubules upon activation via RhoA. Microtubules connect pentagonal quasicrystal neurotransmitter receptors (Gardiner 2015) to octagonal quasicrystal nuclear pore complexes (Gardiner 2018). If microtubule dynamics are disrupted this connexion will be at risk. Indeed nuclear pore complexes appear important in familial and sporadic neurodegenerative disease (Coyne and Rothstein 2022).

It is of interest to note the relationship between β -amyloid precursor protein expression and epilepsy (Sheng et al. 1994). People with epilepsy show more amyloid pathology and cognitive decline (Romoliet al. 2021). It is possible that constitutive activation of neurotransmitter receptors by amyloid induces electrical overload in the nervous system (Bertrand 2002).

Microtubules and Depression

Alzheimer's is associated with depression (Martinez-Hernandez 2022) which is likely to be due to a collapse of prestress in the microtubule/actin cytoskeletal system of neurons. Neuropsychiatric symptoms In Huntington's disease is common and tends toward anxiety, agitation and apathy. These are independent of dementia and chorea (Paulsen et al. 2001). An appreciable proportion of Charcot-Marie-Tooth disease sufferers show general distress and depression. This proportion is related to disease severity and consumption of antidepressants suggesting that it is the disease which is contributing to the depression (Bellofatto et al. 2023). People suffering amyotrophic lateral sclerosis (ALS) display neurological conditions: motor neuropathy and frontotemporal dementia. They may also display psychiatric conditions:



schizophrenia, psychosis and depression (Zucchi et al. 2019). I do not think psychosis is necessarily associated with schizophrenia. Various dysfunctions of the cytoskeletal tensegrity network and hence cognition must inevitably lead to hallucinations and troubled mentality.

Hyperstable Microtubules

Both collapsed microtubule compression-resistance, as seen in Alzheimer's disease, Parkinson's disease and ALS as well as hyper-compression-resistant microtubules, as seen in hereditary spastic paraplegia (HSP), lead to neurodegeneration (Dubey et al. 2015). Two groups of people with HSP have increased risk of schizophrenia: those with Kjellin's syndrome and those with SPG4-HSP (McMonagle et al. 2006). SPG4-HSP is due to mutation of the gene for Spastin, which is a microtubule severing protein. Microtubules that are severed often undergo rapid depolymerisation. So, neuronal microtubules in people with this mutation will tend to be longer. This leads to regions of higher stress in the cytoskeletal network and thus, under this model, the schizophrenia.

Brain asymmetry is greater in those with schizophrenia and related to avoidance and apathy (Núñez et al. 2017). This, again, shows that breaking the tensegrity symmetry leads to pathogenesis. The only known effective anti-schizophrenia drug, clozapine, destabilises microtubules (Hino et al. 2021) which is perhaps no surprise. Interestingly, there was an overall protective effect of schizophrenia polygenic risk score on "Alzheimer's with psychosis" risk (DeMichele-Sweet et al. 2018). This suggests that a decrease in internal cytoskeletal prestress may precede amyloid plaque build-up extracellularly. At least one intramembrane protein (Notch) is activated by mechanosensitive proteolysis (Gordon et al. 2015), and it seems possible that the proteolytic cleavage of APP to form amyloid subunits is force-dependent.

Parkinson's Disease

Parkinson's disease appears to be a type of amyloidosis featuring accumulation of fibrils of α -synuclein (Lewy bodies and neurites) and

can thus be seen somewhat as an Alzheimer's variant, or vice versa (Araki et al. 2019). In Parkinson's α -synuclein is cleaved to a broad spectrum of fragments with currently little-known properties (Bluhm et al. 2021), possibly in a mechanosensitive manner. Dopaminergic neuronal systems are particularly hit in Parkinson's, cholinergic in Alzheimer's. Though infusing rats with β -amyloid disrupts both systems (Itoh et al. 1996) and Parkinson's often has a cholinergic component (Bohnen and Albin 2011).

The accumulation of amyloid intracellularly in both Lewy neurites and Lewy bodies may in part explain the wide variety of symptoms which accompany Parkinson's. Lewy bodies will compress cytoplasm through the addition of matter within cells causing cytoskeletal tensegrity collapse and depression. Lewy neurites may promote schizophrenia-like behaviours due to hyperstable cell processes. Growing amyloid fibres induce force comparable to that generated by actin and microtubules polymerising (Herling et al. 2015) and appear quite stable, not easily depolymerised. Thus they may act as thermal ratchets, using Brownian motion to extend. Indeed schizophrenia has been shown to affect neurite morphology (Mizutani et al. 2019). It is almost certain tensegrity is crucial here: microtubules known to be involved in Parkinson's with mutation of the parkin microtubule-stabilising protein gene leading to disease (Feng 2006).

Dopamine receptors are heptagonal so they may form quasicrystals with a periodicity of seven. In Alzheimer's the pentagonal cholinergic neurotransmitter receptors are at jeopardy from pentagonal amyloid, in Parkinson's maybe the heptagonal G-protein coupled receptors (GPCRs) which are involved in dopaminergic signalling. Indeed 5-, 7- and 8-periodicity structures can arise from β -amyloid peptides (Durell et al. preprint) and α -synuclein is involved in the correct folding of heptagonal-faced clathrin-coated vesicles (Vargas et al. 2020). GPCRs have affinity for hexagonal-phase lipid membrane (Escribá et



al. 2007), which also hints at geometric ordering.

Actin and Neurology

Cofilin is an F-actin destabilising protein. In Alzheimer's it is sequestered into cofilin-actin rods, disrupting normal actin cytoskeleton dynamics and blocking cellular transport (Bamburg and Bernstein 2016). The sequestration of the destabilising protein will act to increase F-actin overall length, thus reducing stress in the cytoskeletal network leading to depression, under this model. Indeed this is what is observed. There is substantial evidence that lineally significant depression is a risk factor for developing Alzheimer's disease (Sáiz-Vázquez et al. 2021). Concomitantly actin polymerisation is decreased in the anterior cingulate cortex of patients with schizophrenia, with a decrease in F-actin and an increase in G-actin (Bhambhani et al. 2017). This will shorten actin filaments, leading to increased stress in the cytoskeletal tensegrity network.

Bipolar

Proteins which cross-link microtubules and actin filaments are involved in schizophrenia, depression and bipolar. Bipolar can occur with Parkinson's disease, frontotemporal dementia and other neurological conditions (Digiovanni et al. 2022) and indeed there can be similar dysfunctions in both major depressive disease and schizophrenia (Zaharija et al. 2022). Microtubules are stabilised by lithium ion (Bhattacharyya and Wolff 1976) which is the "gold standard" treatment for bipolar. Binding of collapsin response mediator protein 2 (CRMP2) to tubulin increases microtubule formation and this binding is decreased upon phosphorylation by Rho kinase [Fukata et al. 2002]. Consistent with genetic linkage data, proteome-wide analysis has revealed increased expression of CRMP2 in post-mortem brains from individuals with both schizophrenia and depression (Marchisella et al. 2016) showing it is a link between the two. Mutations in the actin/microtubule cross-linking proteins MACF1 (Pol-Fuster et al. 2021) and

adenomatous polyposis coli protein are also associated with mental illness.

Treatments

"Whilst there may be some situations when the use of paternalism can be justified in mental health care, it should be exercised with caution. When there is disagreement between nurse and patient on what is considered to be in the patient's best interests, it should not be assumed that the patient is wrong or irrational" (Breeze 2001).

There is increasing interest in the use of tensegrity principles in physiotherapy and osteopathy. People who are sad or depressed show specific changes in posture (Rosario et al. 2014) and if these are improved, affective symptoms are reduced (Wilkes 2017). It seems possible that small-scale tensegrity (in neurons) can communicate with large-scale tensegrity at the level of muscle, connective tissue, bone, through fractal nesting. In the same vein therapeutic massage can be a useful treatment for behavioural disturbances in people with dementia (Avila and Rodriguez-Mansilla 2015).

During the course of the COVID pandemic (in 2021) the rate of prescription of psychotropic drugs to Australian children jumped significantly (Wood et al 2023). Whilst drugs have their place, talk therapies are able to treat aspects of schizophrenia which drugs cannot reach (Kurtz 2023). Long-term (6 month) meditation practice in persons with mild cognitive impairment or mild Alzheimer's disease leads to salutary changes in cortical thickness and grey matter volumes. Most of these changes are observed in the brain areas related to executive control and memory that are prominently at risk in neurodegenerative diseases (Dwivedi et al. 2021). Meditation helps with Parkinson's (Kwok et al. 2023). It is interesting that psychology is now looking at "social tensegrity" as *res* (Primus 2023). Perhaps neuronal cytoskeletal tensegrities are connected up beyond the individual. Certainly mental health has a social component.

It is interesting to note that Victorian-era asylums had high rates of recovery from mental illness when compared to modern-day

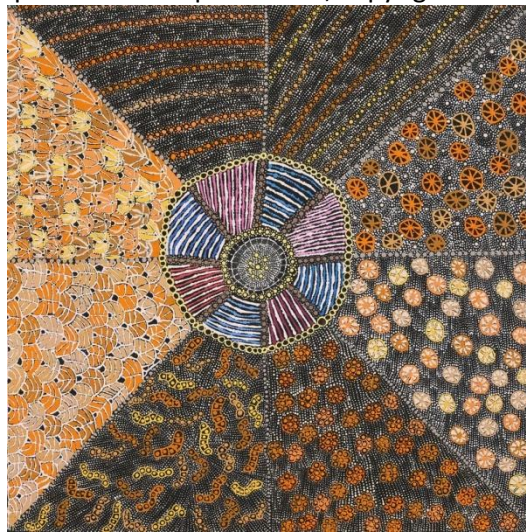


institutions (Renvoize and Beveridge 1989; Hill and Laugharne 2003).The asylums used radically different treatments to those seen today, for example putting on pageants. However there was also high mortality. In an ideal world we should strive to combine the high cure rate of the Victorian asylum with the relative safety of today's approach to mental illness.

Even with Alzheimer's there is hope. Some asymptomatic people die with tangles and plaques but have managed to rewire their brains to maintain function (Wilson 2017).

At some point Science, Spirituality and the Arts must meet. In 2018 The Powerhouse Museum, Sydney, hosted an exhibition of Australian Indigenous paintings juxtaposed with cell biology micrographs. There were/are many similarities between the two groups of images. Indigenous Australia, the World's oldest continuous culture, is a keen observer of the biological world. Figure 1 shows a painting with octagonal symmetry (Nuclear Pore Complex) and possible microtubules and actin filaments and more...

Figure 1: "LukarraraJukurrpa" Desert Fringe-rush Seed Dreaming by Hilda Nakamarra Rogers. Painting reproduced with permission, copyright is with the artist.



Conflict of Interest

I have no conflict of interest.

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