Neurodegeneration: The Sites of Onset Predicted by Wireless Communication Model

Frank Lee
eMail: frank@geon.us
Website: http://www.geon.us

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Abstract

According to the Wireless Communication Model proposed in Paper 1, the receiving neurons for electromagnetic (EM) waves should display subthreshold oscillations so that the EM waves can push the membrane potential above threshold to achieve large scale synchronization. These receiving neurons are vulnerable to hyperexcitability and thus could be the sites of onset for neurodegeneration. Based on this notion, the initial sites for major neurodegenerative disorders have been identified. Each site is known to display subthreshold oscillations at a particular frequency band, except the striatum which shows plateau depolarizations. Instead of a specific brain rhythm, the striatum may respond to overall brain activity, consistent with its possible role in pleasure principle: seek pleasure, avoid pain.

- Alzheimer's disease: entorhinal cortex, theta band.
- Parkinson's disease: subthalamic nucleus, beta band.
- Amyotrophic lateral sclerosis: motor cortex, beta band.
- Frontotemporal dementia: anterior cingulate cortex, alpha band.
- Memory consolidation deficits: locus coeruleus, 0.3 - 3 Hz.
- Motivational deficits: striatum, plateau depolarizations.

Introduction

Despite intensive research in the last several decades, the initial sites of neurodegeneration remain unclear. For instance, Alzheimer's disease was thought to begin in the entorhinal cortex (EC), but recent studies suggest that locus coeruleus (LC) could degenerate even earlier than EC (Braak et al., 2011). Parkinson's disease is characterized by the loss of dopaminergic (DA) neurons in substantia nigra pars compacta (SNc). However, for the treatment of Parkinson's disease, the subthalamic nucleus (STN) has emerged as the primary target of deep brain stimulation (Hickey and

Stacy, 2016). STN exhibited significantly increased spontaneous firing in the MPTP model of parkinsonism (Bergman et al., 1994). Could Parkinson's disease arises from neuronal hyperexcitability in STN?

Paper 4 suggests that neurodegeneration may originate from BDNF deficiency, which will cause miR-132 deficiency, resulting in excess Tau proteins (especially the 4-repeat isoform), and consequently hyperexcitability. Different neurodegenerative disorders may begin in distinct hyperactive regions. For Alzheimer's disease, Tau-mediated hyperexcitability may occur initially in EC or LC while for Parkinson's disease the STN could be affected first. This paper will identify the initial sites for major neurodegenerative disorders, based on the Wireless Communication Model proposed in Paper 1. It will be shown that each site of onset is responsible for sensing a particular brain rhythm, except the striatum which may react to overall brain activity.

Predictions of the Wireless Communication Model

According to the Wireless Communication Model, the long range synchronization is mediated by electromagnetic (EM) waves, which by themselves are insufficient to elicit a spike from the resting membrane potential. The receiving neurons for EM waves must already be depolarized to a subthreshold value by synaptic inputs and/or extracellular electric fields. The EM waves can then push the membrane potential above threshold to achieve large scale synchronization. Since the receiving neurons are constantly in a depolarized state, a slight elevation in membrane potential or aberration in excitability may cause them to fire. Thus, they should be vulnerable to hyperexcitability and could be the initial sites of neurodegeneration.

There are many different causes for hyperexcitability. Alteration at synapses is a classic example. However, the receiving neurons are vulnerable to Tau-mediated hyperexcitability which occurs at the axon initial segment (AIS), not synapses. As proposed in Paper 2, the AIS of receiving neurons should contain "microtubule antennas" for converting EM waves into neuronal excitability. The dynamic association between microtubule antennas and AIS membrane regulates excitability, which in turn is modulated by Tau proteins. The Tau-mediated hyperexcitability often results in Tau pathology, but synapse-mediated hyperexcitability rarely leads to Tau pathology (see next paper).

Then, where are these receiving neurons located? The Huntington's disease (HD) may offer some clues. HD is caused by mutations in the huntingtin gene (*HTT*). The mutant huntingtin contains expanded glutamine repeats, capable of interacting with the splicing

factor SRSF6, leading to increased 4R Tau and total Tau protein level (Fernández-Nogales et al., 2014). In addition, huntingtin plays an important role in enhancing the transport of BDNF-containing vesicles from the cell body to synapses (Gauthier et al., 2004). The mutation of huntingtin will reduce BDNF level at synapses, thereby impairing BDNF-TrkB signaling.

Huntingtin is expressed ubiquitously across the brain, but only a number of brain regions are selectively affected. Among them, striatum is the most severe, partly due to its heavy dependence on BDNF transport (Zhao et al., 2016). Other areas impaired by HD include EC (Braak and Braak, 1992), STN (Callahan and Abercrombie, 2015), LC (Zweig et al., 1992), and cerebral cortex (Vuono et al., 2015), particularly the primary motor cortex and anterior cingulate cortex (ACC) (Thu et al., 2010). These vulnerable regions are likely to contain the receiving neurons, and thus could be the sites of onset for other neurodegenerative disorders. Interestingly, neurons in each region have been shown to display subthreshold oscillations at a specific frequency band, except the striatum which shows plateau depolarizations.

Theta Rhythm, EC and Alzheimer's Disease

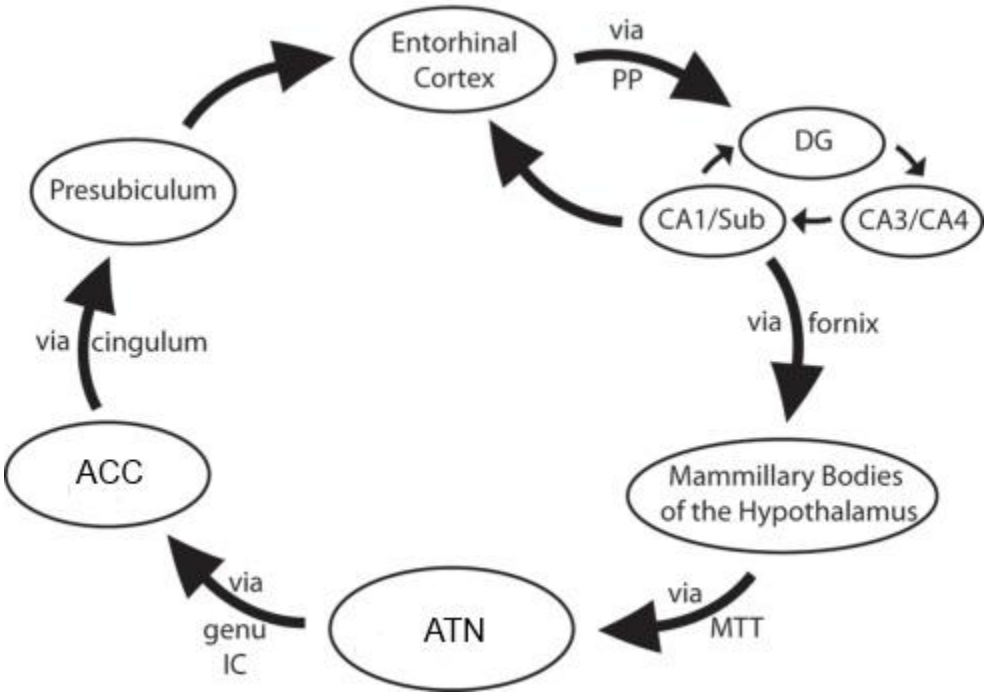

Figure 1. The Papez circuit. DG, CA1 and CA3 are the subregions of hippocampus. ATN: anterior thalamic nuclei; ACC: anterior cingulate cortex. [Source: Augustinack et al., 2010]

The theta rhythm is believed to originate from the medial septum, which has reciprocal connections with the hippocampus. Their bidirectional interaction generates the core theta rhythm (Hangya et al., 2009; Kang et al., 2015). In the Papez circuit (Figure 1), several structures contain large populations of theta neurons (which oscillate at the theta band) such as EC (Schlesiger et al., 2015), ATN (Jankowski et al., 2013), and ACC (Womelsdorf et al., 2010). These theta neurons can be recruited by the septum-hippocampus network to join the large scale theta synchronization. In terms of wireless communication, the medial septum represents the transmitting area, while the theta neurons within the Papez circuit may act as both receiving and transmitting neurons, and thus susceptible to Tau-mediated hyperexcitability and Tau pathology (Aggleton et al., 2016). The stellate cells of EC layer II are highly excitable. They regularly exhibit subthreshold oscillations at the theta band such that minimal elevation (1-3 mV) of membrane potential is sufficient to generate spikes (Alonso and Klink, 1993).

Slow Oscillations, LC and Memory Consolidation

Like the stellate cells in EC layer II, LC neurons are also very excitable. In brain slices prepared from both neonatal and adult rats, they displayed subthreshold oscillations at the frequency between 0.3 and 3 Hz. Spontaneous firing was commonly observed (Christie et al., 1989; Alvarez et al., 2002). Such high excitability, and other possible factors, make LC even more vulnerable to Tau pathology than EC. In many cases, hyperphosphorylated Tau proteins appear in LC earlier than EC (Braak et al., 2011; Braak and Del Tredici, 2011; Elobeid et al., 2012). However, this does not imply that Alzheimer's disease begins in LC, rather than EC.

Alzheimer's disease is usually defined as a disorder of memory formation in which the Papez circuit plays a critical role. By contrast, LC is involved in memory consolidation (Zornetzer and Gold, 1976; Mello-Carpes et al., 2016; Sara, 2010). Moreover, the Papez circuit synchronizes at the theta band while LC neurons oscillate at slow frequency. These observations suggest that EC and LC may represent the initial sites for distinct diseases. Indeed, there are cases that hyperphosphorylated Tau proteins are substantial in EC but only minimal in LC. As discussed in the following sections, Tau pathology is not unique for Alzheimer's disease. Other neurodegenerative disorders may also arise from hyperphosphorylated Tau proteins.

Beta Rhythm, STN and Parkinson's Disease

Parkinson's disease is characterized by the loss of dopaminergic (DA) neurons in substantia nigra pars compacta (SNc). This region exhibits spontaneous firing (Puopolo el al., 2007). However, SNc rarely displays Tau pathology, indicating that this region is not involved in long range synchronization. On the other hand, the Tau gene *MAPT* has been demonstrated to associate with Parkinson's disease (Bras and Singleton, 2009; Robakis et al., 2016). If Parkinson's disease originates from Tau-mediated hyperexcitability, it must begin in a region upstream to SNc.

There is substantial evidence that the loss of DA neurons in SNc arises from glutamate-mediated excitotoxicity (Blandini et al., 1996; Ambrosi et al., 2014). The subthalamic nucleus (STN) provides major glutamatergic inputs to SNc (Lee and Tepper, 2009). Moreover, STN exhibits spontaneous firing (Bevan and Wilson, 199) and plays a critical role in the large scale synchronization at the beta band (Ahn et al., 2016) - the brain rhythm responsible for motor timing. Computer simulation suggests that the beta rhythm is generated by bidirectional interaction between STN and external Globus Pallidus (GPe), together with excitatory input from the motor cortex to STN (Holgado et al., 2010; Pavlides et al., 2015). The idea that STN could be the initial site for Parkinson's disease is further supported by the observation that excessive beta is associated with Parkinson's disease, resulting from hyperactive STN (Kühn et al., 2006).

Since STN acts as both receiving and transmitting area during beta synchronization, it should contain "microtubule antennas", and thus prone to Tau pathology. Consistent with this prediction, significant neurofibrillary tangles have been found in the STN of progressive supranuclear palsy (PSP), corticobasal degeneration, argyrophilic grain disease and advanced Alzheimer's disease (Mattila et al., 2002; Ishino and Otsuki, 1975). The symptoms of PSP resemble Parkinson's disease (Dickson et al., 2007).

Beta Rhythm, Motor Cortex and ALS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that affects motor neurons in the motor cortex, brain stem, and spinal cord. It is characterized by the inclusion bodies composed of mainly abnormal TDP-43 - a protein involved in the biogenesis of several microRNAs, including miR-9 and miR-132 (Paper 4). Pathologically, ALS may be divided into Tau-positive (ALS-T) and Tau-negative (ALS-N). In ALS-N, Tau pathology is sparse. In ALS-T, such as the Guam-type, neurofibrillary tangles are abundant in the primary motor cortex (Hof and Perl, 2002).

Compelling evidence indicates that ALS arises from hyperexcitability in the motor cortex (de Carvalho et al., 2014; Braak et al., 2017). As noted above, motor cortex is required for the generation of beta rhythm, which is also implicated in ALS (Proudfoot et al., 2017). The motor neurons within the motor cortex, known as "Betz cells", do not display Tau pathology. They are unlikely to initiate ALS (Sasaki and Maruyama, 1994). Like the DA neurons in Parkinson's disease, motor neurons in ALS are impaired by glutamate excitotoxicity (de Carvalho et al., 2014). Therefore, ALS may begin in the neurons that send glutamatergic inputs to Betz cells. These neurons could be located in the primary motor cortex oscillating at the beta band (Lindenbach and Bishop, 2013; Lacey et al., 2014).

Mu (Alpha) Rhythm, ACC/AIC and FTD

Frontotemporal dementia (FTD) is the clinical manifestation of frontotemporal lobar degeneration (FTLD), which is characterized by the loss of von Economo neurons (VENs). Clinically, FTD may be divided into one behavioral variant (bvFTD) and two language variants: semantic dementia and progressive non-fluent aphasia. bvFTD accounts for half of all FTD. Pathologically, FTLD may be either Tau-positive or Tau-negative, with roughly equal prevalence. The Tau-negative FTLD is dominated by TDP-43 pathology (Seeley, 2008).

VENs are present predominately in anterior cingulate cortex (ACC) and fronto-insular cortex which is part of anterior insula cortex (AIC). Both ACC and AIC are known to play important roles in social behavior. They are activated by resentment, deception, guilt and the feelings of empathy for the suffering of others (Allman et al., 2011). An offender with relatively low ACC activity is more likely to be rearrested than those with high activity in this region (Aharoni et al., 2013), possibly due to lack of empathy. Autism is also characterized by social deficits. However, in autism patients, ACC has either increased or reduced VEN density (Simms et al., 2009) and fronto-insular cortex contains larger number of VENs, compared to controls (Santos et al., 2011). Further investigations are required to clarify the role of VENs in autism and FTD.

ACC is one of the regions that generate alpha rhythms (8 - 12 Hz) (Connemann et al., 2005). The mu rhythm refers to the alpha rhythm measured over the sensorimotor cortex. Recently, it has been found that the amplitude of mu rhythm positively correlates with activities from ACC and AIC (Yin et al., 2016). Thus, VENs could be involved in the processing of mu rhythms. Higher mu activity has been shown to associate with autism (Xiang et al., 2016). Interestingly, ACC and AIC are responsible

for the integration of all kinds of sensory information, but VENs have sparse dendritic trees (Watson et al., 2006). Could they receive mainly "wireless inputs"?

EM Field Density, Striatum and Motivation

Striatum is the most vulnerable region to Tau pathology in Huntington's disease (Vuono et al., 2015) and Parkinson's disease (Wills et al., 2010; Wills et al., 2011). It is also severely affected in FTD (Kim et al., 2007; Halabi et al., 2013). These observations indicate that the striatum may act as a receiving area during wireless communication. However, the striatum contains mostly medium spiny neurons (MSNs) which do not have any preferred oscillating frequency. Unlike other receiving neurons that exhibit subthreshold oscillations at a particular frequency, MSNs display plateau depolarizations, called "up states", which are separated by very negative membrane potential, referred to as the "down state". MSN firing is possible only during up states (Murer et al., 2002; Zold et al., 2012).

The striatum is known to play a central role in **action selection**: Go or NoGo. The selection of "Go" generates the motivation to act. Whether the MSN firing leads to Go or NoGo depends on the dopamine level in the striatum. Higher dopamine level promotes the decision for "Go" (Bromberg-Martin et al., 2013; Ikemoto et al., 2015). Thus, dopamine deficiency would result in lack of motivation. In the brain, dopamine is released mainly from two areas: SNc and ventral tegmental area (VTA). Both regions may influence action selection. However, it is the loss of DA neurons in SNc that causes the motivation deficits in Parkinson's disease (Drui et al., 2014). Impairment in the striatum can also cause motivation deficits, as observed in Huntington's disease.

In later papers, evidence will be presented for the hypothesis that the feeling of pain or pleasure depends on overall brain activity, which in turn gives rise to different levels of electromagnetic (EM) field density. Higher density of EM fields may cause more painful feeling. MSNs may convert the EM density into action. High EM density leads to NoGo, while low EM density favors Go. This could be the physiological basis for Freud's pleasure principle: seek pleasure, avoid pain.

Summary

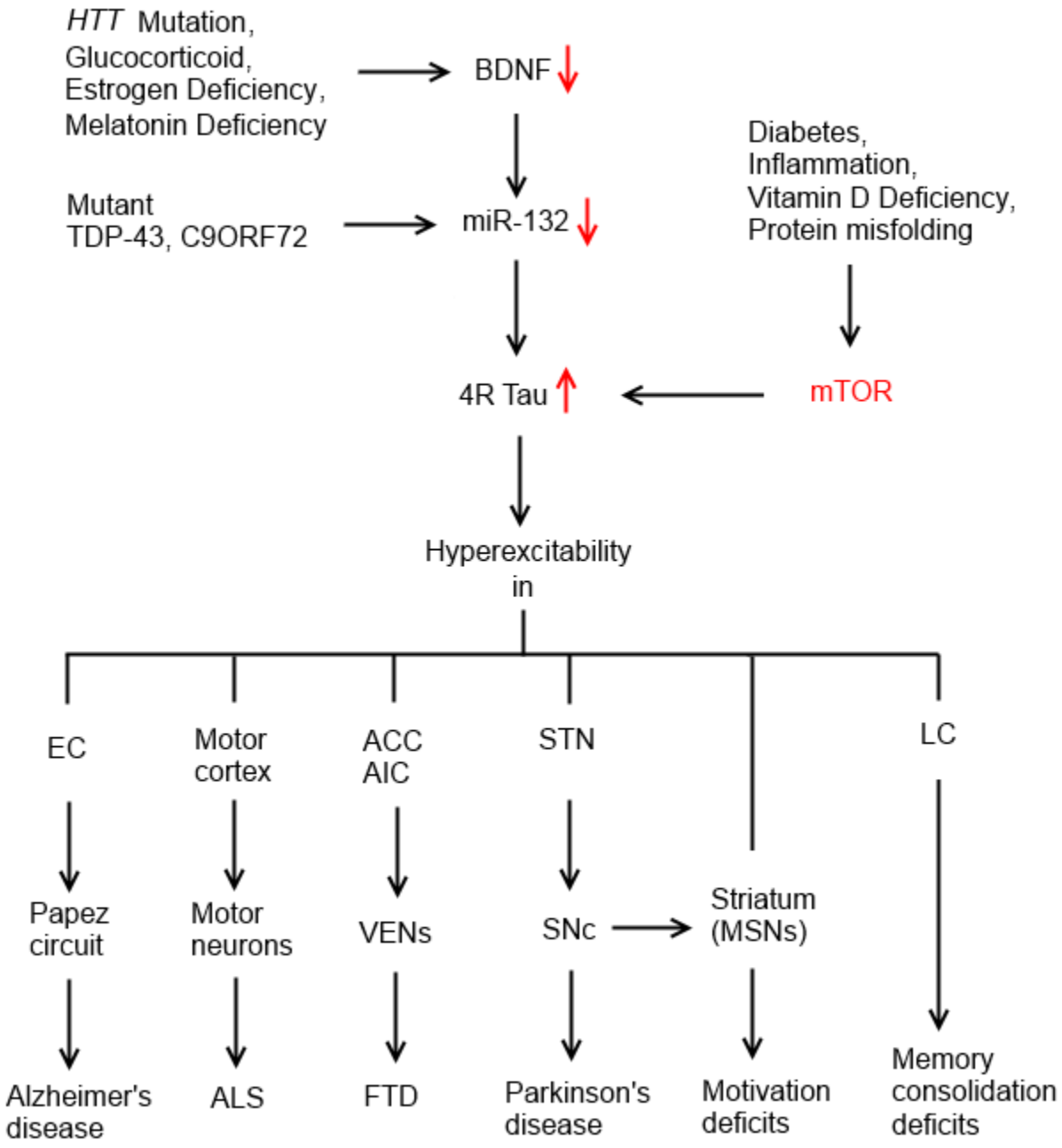

Figure 2. The proposed pathogenic cascade for neurodegeneration. See text for detail.

Figure 2 summarizes the proposed pathogenic cascade for neurodegeneration. Each component in the cascade may be affected by several factors. For instance, BDNF deficiency could be caused by *HTT* mutation, glucocorticoid elevation (Suri and Vaidya, 2013; Wosiski-Kuhn et al., 2014), estrogen deficiency (Carbone and Handa, 2013) and melatonin deficiency (Imbesi et al., 2008; Zhang et al., 2013; Rudnitskaya et al., 2015). Glucocorticoid level may be elevated by psychological

stress, which is a risk factor for Alzheimer's disease via Tau hyperphosphorylation (Rissman, 2009; Sotiropoulos et al., 2011; Sotiropoulos and Sousa, 2016).

In addition to BDNF deficiency, miR-132 reduction may result from mutant TDP-43 or C9ORF72 (Paper 4). miR-132 reduction leads to increased Tau level, especially the 4R isoform. Tau expression is also regulated by mTOR, whose activation depends on a variety of factors, such as diabetes (high glucose level), inflammation (increased cytokines), vitamin D deficiency, and protein misfolding (Paper 3).

The mechanisms from hyperexcitability to pathologic Tau, TDP-43 and α-synuclein will be discussed in the next paper.