The Limited Spread of Progressive Neuronal Damage from Cortex to Subcortical Regions: A Review

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1 Abstract

Globally, almost 44 million people suffer from progressive neurodegenerative diseases, while another 69 million suffer from traumatic brain injury. These pathologies cause the spread of Progressive Neuronal Damage (PND) across neural networks and affect the associated brain structures, causing significant cognitive and functional decline. Defining the strength of these neural networks is important as strength of the network is directly proportionate to intensity and speed of PND across it. Adopting a review approach, this study examines a number of clinical reports and draws conclusions regarding the strength of neural networks, concluding that cortico-subcortical networks are relatively weak in comparison to subcortico-cortical connections. This is accompanied by the conclusion that only limited spread of PND from the cortex to the subcortical regions occurs.

Keywords: Progressive Neuronal Damage - Cortex - Subcortical Regions - Hypometabolism - Neural Network

2 Introduction

Progressive neuronal damage (PND) is an umbrella term for large-scale, progressive degradation of neural networks caused by three types of pathology: neurodegenerative diseases (where PND is called neurodegeneration), strokes (where PND is called diaschisis), and Traumatic Brain Injury or TBI (where PND is called inflammation). PND can spread across neural networks and cause hypometabolism of different parts of the brain (Seeley et al., 2009), in cortical structures such as the frontal lobe, temporal lobe, etc., as well as deep subcortical structures like the thalamus, caudate nuclei, etc. This causes functional deficits: affected cortical regions usually cause deficits in speech, cognition and voluntary movements, while affected subcortical regions usually cause deficits in balance, posture, and involuntary movement.

Currently, there are no known ways to stop the spread of PND, only ways to improve the symptoms displayed by the patients (Chen and Pan, 2014). However, to understand how to treat PND, it is of utmost importance to understand the speed and intensity at which it spreads across neural networks between brain regions (Iturria-Medina and Evans,

2015). Adopting a review approach, this paper theorizes that the weak nature of cortico-subcortical networks results in the cortex limiting the spread of PND. However, the strong subcortico-cortical networks result in the subcortical regions not limiting (globalising) the spread of PND to adjoining subcortical regions and distant cortical regions.

The most common method to track functional deficits in response to pathology (and thus understand the reaction of different brain regions to neural death) is Lesion Symptom Mapping (LSM), that is, tracking functional changes in patients with lesions in different parts of the cortex (Bates et al., 2003). However, to expand the scope to include not just lesion, but also non-lesion based patholiges, this study works off a consortium of clinical reports, adopting a review approach. Furthermore, this study tracks hypometabolic locations in the brain rather than observed functional deficits, thus employing a quantitative measure over a qualitative one.

3 Literature Review

Mountcastle (1997) formulated the widely accepted modular theory of the brain, which hypothesizes that the cortex is organised into several strongly interconnected vertical functional regions, called modules. Further studies (Chen et al., 2008; Meunier et al., 2009) concluded that each module was weakly interconnected horizontally to the other modules, meaning that the cortex was a weakly interconnected patchwork of densely intra-connected modules. This theory heralded massive neurological advancements including reconstructing functional neural networks within the brain (Januszewski et al., 2018).

While we have gained a reasonably strong understanding of neural networks in the brain through their mapping and reconstruction using computational methods, we are yet to gain a strong insight into the strength of these networks.

Determining neural network strength is of utmost importance; PND spreads more quickly and with greater intensity along stronger functional neural connections. In cases where the causal region and affected region are weakly interconnected, patients show only mild to moderate deficits relating to the affected region. Conversely, in cases where the causal and affected region were strongly interconnected, patients experienced strong functional deficits relating to the affected region (Yates, 2012).

To understand the strength of functional neural networks and, by extension, the strength and intensity of PND along these networks, this study adopts a novel method, examining a consortium of clinical reports of pathology to different regions of the brain and the metabolic changes in the affected regions, thus tracking the spread of PND in the cortex and subcortical regions, as well as between subcortical regions and cortical modules.

There are many clinical studies which discuss the effect of subcortical pathology on adjoining subcortical regions and cortex. Jeffery et al. (2000) studied the metabolic effects of subcortical lesions on adjoining cortical areas, finding extensive hypometabolism in the cortex, as well as the adjoining subcortical regions. Du et al. (2005) found that subcortical white matter lesions were the main cause of atrophy in the cortical regions. Other studies researched the effects of cortical pathology on adjoining cortical regions and subcortical regions. Risacher and Saykin (2013), outlined the metabolic effects of various dementia related pathologies in the cortex, concluding that the metabolic effects were heavily localised to the causal region, and did not spread to other cortical regions or subcortical regions. Kushner et al. (1984), studied the effects of parietal stroke on

the other regions of the brain, concluding that both adjoining regions of the cortex and distant subcortical regions like the cerebellum, exhibited hypometabolism.

4 Methods

4.1 Data Acquisition

The author conducted a literature evaluation of 200 articles identified on scientific databases such as PUBMED and Google Scholar, retaining only those that subscribed to the pre-conditions listed below:

1. Only English language content

2. Quantitative analysis that is, hypometabolism (PET) was required

3. Original data

4. Clear causal locations (studies on mood disorders were thus not included)

Thirteen Articles were chosen for the study and were analysed using a review methodology.

Greater hypometabolism of the affected region was taken to mean greater strength of neural networks from causal region to affected regions. The converse was assumed to mean a weaker neural network.

4.2 Definitions

The brain was considered to be made up of two broad Divisions: the cortex and the subcortical regions. The cortex was defined to be the outermost part of the brain; made up of the frontal lobe, the temporal lobe, the occipital lobe, the parietal lobe, and by extension, the subregions constituting the four lobes. The subcortical regions were defined to include the hypothalamus, the thalamus, the hippocampus, the amygdala, the cerebellum, the brainstem (pons and medulla), the basal ganglia (the substantia nigra, the cingulate gyrus, the caudate nuclei), the putamen and the white matter structures.

4.3 Statistical Analysis

Based on the data acquired, both the subcortical regions and the cortex were given a Globalisation Score (GS) which measured the strength of their inter-connectivity and intra-connectivity.

The Globalisation Score of the Cortex and the Subcortical Regions was taken to be the average of the scores of all constituent regions.

$$GS = \frac{\sum S_{region}}{n}$$

5 Results and Discussion

In cases where the basal ganglia was the causal region, including Huntington's Disease (HD), strokes and lesions, the Prefrontal Cortex (PFC), particularly the dorsolateral and orbitofrontal region, expressed strong hypometabolism (McMurtray et al., 2008; Levy and Dubois, 2006). Hippocampal pathology, such as Hippocampal Sclerosis (HS) and AD almost always immediately affected the adjoining cortical regions: the temporal lobe and the trans-entorhinal cortex (Frisoni et al., 1999). While thalamic strokes did not affect any specific region of the cortex, it caused moderate globalised hypometabolism across the ipsilateral cortex (Baron et al., 1986; Pappata et al., 1990). Amgydala lesions were observed to cause significant hypometabolism in the frontal lobe and the basal ganglia.

When the cortex was the causal region, strong hypometabolism was observed in the causal region, with low to moderate hypometabolism in adjoining cortical regions. The only exceptions to this rule were the case of cortical stroke in the parietal lobe, which produced significant hypometabolism in the cerebellum (Kushner et al., 1984), and in AD from the entorhinal cortex to the hippocampus, which exhibited significant hypometabolism (Meguro et al., 1999).

Analysis of Parkinson's Disease (PD) progression indicated that the disease almost immediately progressed from the causal subcortical regions (substantia nigra and medulla) (Braak et al., 1996) to the motor cortex. Similarly, in Alzheimer's Disease (AD), after spreading between the entorhinal cortex from the hippocampus, it spreads to other cortical regions- the parietal, temporal, and frontal lobe- causing significant cognitive deficits. Both PD and AD, being progressive disorders, did not show rebound spread of PND in the subcortical regions from the cortex.

The GS of the cortex was found to be 2.2, while that of the subcortical regions was 3.875; the subcortical regions exhibited 76 percent greater interconnection than the cortex.

The limited interconnection from the cortex to the sub-cortical regions is best explained by the modular organisation of the cortex (Mountcastle, 1997). The cortex is organised into columns made up of 6 neuronal layers, each with the receiving dendritic ends facing downwards and the conducting axonal endings facing upwards. These cortical columns are then organised into modules, which have excellent vertical intra-connectivity but weak horizontal inter-connectivity. Layers 5 and 6 are interconnected with subcortical structures including the hippocampus, the thalamus, and the cerebellum, and are part of cortico-subcortical functional loops, while layers 1 to 4 are involved in intra-modular, and to a limited extent, inter-modular connections. This means that only 33 percent of the cortex is interconnected with the subcortical regions, so a smaller proportion of the cortex plays a role in the cortico-subcortical functional networks. Furthermore, the subcortical regions have a near monopoly on neurotransmitter production, including dopamine, serotonin and acetylcholine (Hornung, 2003; Picciotto et al., 2012; Juárez Olguín et al., 2016), allowing message conduction from the subcortical regions to cortical regions to be markedly stronger.

There are two noteworthy exceptions of cortical pathology causing globalised effects. Pathology to the parietal lobe and the entorhinal cortex caused strong hypometabolism in the connected subcortical regions, the cerebellum and hippocampus respectively. Due to the strong hypometabolism in the subcortical regions, these exceptions received Scores of 4, while instances of pathology to other regions of the cortex received scores of 1. These exceptions drive up the Globalisation Score of the cortex from 1 to 2.2, as evident in the table.

A probable benefit of weak cortico-subcortical neural networks is that it confers a survival advantage: while the cortical regions are important for intelligent skills like cognition and speech, they are not essential to survival. The subcortical regions are, however, solely responsible for survival; they maintain homeostasis, control involuntary movements, heartbeat, respiration and control neurotransmitter production. Thus, due to the weak cortico-subcortical functional networks, PND does not spread from an affected area in the cortex to the subcortical regions and thus endanger the survival of the organism.

6 Conclusion and Future Objectives

From the studies analysed, it was clear that the weak nature of functional networks from the cortex to the subcortical regions results in the cortex limiting the spread of PND to the adjoining cortical regions and the subcortical regions. However, the same is not true of the subcortical regions; strong functional networks extend to adjoining subcortical regions and distant cortical regions, means that the spread of PND is globalised.

If the study were to be replicated, it would be executed using machine learning tools on MRPET scans drawn from neurodegenerative neuroimaging datasets. Based on a graph-theory based method outlined by Chen et al. (2008), cortical thickness will be used to build a graph network between the different regions of the brain. The nodal strength would then have to be judged by an algorithm. Limitations to this method, include the intensive pre-processing required to normalize the image data, as well as the need for powerful systems to process data, which is usually stored in extremely heavy DICOM files. However, a computational approach would run off larger datasets, and draw further correlations which would not be revealed in smaller datasets.

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