

A Hierarchical Model for Autism Spectrum Disorder (HMASD)

Ghasem Sadeghi Bajestani,^{1*} Ali Sheikhani,¹ Mohammad Reza Hashemi Golpayegani,² Farah

Ashrafzadeh,³ and Paria Hebrani⁴

¹Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, IR Iran

²Department of Biomedical Engineering, Amir Kabir University of Technology, Tehran, IR Iran

³Paediatric Neurology Division, Qaem Hospital, Mashhad University of Medical Sciences, Mashhad, IR Iran

⁴Department of Paediatrics, Dr Sheikh Paediatric Hospital, Mashhad University of Medical Sciences, IR Iran

* Corresponding author: Ghasem Sadeghi Bajestani, Department of Biomedical Engineering, Science and Research Branch, Islamic Azad University, Tehran, IR Iran. E-mail: g.sadeghi@imamreza.ac.ir

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Abstract

Background: Autism spectrum disorder (ASD) is a severe behavioral disorder characterized by pervasive impairments in social interactions, deficits in verbal and nonverbal communication, and stereotyped, repetitive patterns of behaviors and interests. Despite recent advances in identifying some genes that may cause autism, its underlying neurological mechanisms are uncertain. ASD is best conceptualized by considering the neural systems that may be defective in autistic individuals.

Objectives: Here, we aim to describe a potential Hierarchical model for ASD. This interesting presented model is based on excitatory and inhibitory characteristics of cortico-cortical networks.

Methods: Jason model is one of the models applied to produce EEG in cortical areas. In this model, a cortical area is modeled with three subpopulations including: excitatory pyramidal cells (output), excitatory interneurons groups, input inhibitory interneuron groups by means of output connections (output connections are limited to cortical planes). The presented hierarchical model for autism spectrum disorder (HMASD) is based on Jason model. HMASD is a hierarchical model of cortico-cortical networks as well as an excitation/inhibition model in sensory, mnemonic, social and emotional systems. In HMASD there are three kinds of outer connections including forward, backward and lateral connections, that their power is controlled by coupling parameters.

Results: HMASD raises the possibility that ASD is related to excitation/inhibition imbalance in cortico-cortical networks. HMASD parameters are possible way for quantization imbalance quality.

Conclusions: The most effected parts in ASD are lateral connections of HMASD. Two-sided connections which are completely symmetric become more active, and cause extra synchronization. On the other hand, due to special characteristic of two-sided connections and their ability to simulate the same phased dynamics, they cause unnatural asymmetry in children's EEG signal. These results are consistent with previous findings suggesting the association of EEG abnormalities in ASD with functional impairment of information interacted in cortical connections.

Keywords: Autism Spectrum Disorder, Hierarchical Model, Brain Behavior, Asymmetry

1. Background

Autism spectrum disorder (ASD) is diagnosed by two core behavioral criteria, unusual reciprocal social interactions and communication, and stereotyped, repetitive behaviors with restricted interests (1). Despite the widespread investigations, yet there are arguments about morphological, applicatory and neurological characteristics of ASD (2), and the neural basis of behavioral variations in ASD is still remained to a great extent unknown. The main question which does not seem to have occurred to autism researchers is that "Is Autism Spectrum Disorder a brain's software problem that makes hardware problems (as secondary effect)?" We believe ASD is indeed a software problem leading to changes in the brain's hardware (3, 4). The common hyperactivation of the amygdala in ASD, but in response to opposite stimuli, demonstrates the complexity of amygdala functionality and its relevance to

social behavior. Subjects with ASD display aversion-related amygdala activation while eye gazing, resulting in eye contact avoidance (5).

2. Objectives

The objective of our research is to describe a potential Hierarchical model for ASD. This interesting presented model is based on excitatory and inhibitory characteristics of cortico-cortical networks.

3. Methods

Neocortex has a 6-layered structure and 3 functional layers including Supra-granular, Granular and Infra-granular. Generally, cortical areas contain two groups of neurons: spiny neurons (pyramidal and spiny stellate

cells), and smooth neurons. Most of the cortical neurons are pyramidal cells which are found in layers 2 to 6, and spiny stellate cells are interneurons which are in mid cortical layers (6, 7). Smooth neurons are GABAergic interneurons distributed in all layers. Cortical neurons can be assumed as small repetitive microcircuits created despite the non-homogeneous cortical of a basic microcircuit. The foundation of the basic microcircuit is on pyramidal cells that receive its excitatory inputs from afferent systems and spiny cells while inhibitory inputs are mostly originated from GABAergic neurons. Jason model is one of the models applied to produce EEG in cortical areas. In this model, a cortical area is modeled with three subpopulations including: excitatory pyramidal cells (output), excitatory interneurons groups, input inhibitory interneuron groups by means of output connections (output connections are limited to cortical planes). In this model, excitatory interneurons can be considered as spiny stellate found in layer 4 that receive direct inputs. Excitatory pyramidal cells and inhibitory interneurons are considered to occupy agranular layers and receive top down and lateral inputs (8).

Excitatory and inhibitory characteristics are modeled through two parameters; $H_{e,i}$ and $\tau_{e,i}$. The interaction between different groups is dependent on the constant that controls the power of outer connections and the total number of synapses is defined by each group. The relation between the parameters are claimed to be and in some papers (9). Jason model abridgment can be seen in Figure 1 (10, 11).

Hierarchical model of cortico-cortical networks can be built directly using Jason model. Different types of these connections are shown in Figure 2.

Connections between regions are made with excitatory pathways. There are three kinds of outer connections; Forward, backward and lateral connections. Their power is controlled by coupling parameters: a^F for forward connections, a^B for backward connections and a^L for lateral connections.

Bottom-up effect: the targets of bottom-up connections and outer inputs are alike.

Top-down effect: Top-down connections create a connection between effects in upper levels to lower levels. Input emotional information is spread to high level regions using top-down and probably lateral connections. Existence of forward and backward connections creates loops that stabilize the system. When backward connections are stronger, damped oscillations change into oscillations which finally become stable.

Lateral connections: lateral connections relate different areas of the levels to one another. They can be single or multiple sided. The main difference between single sided

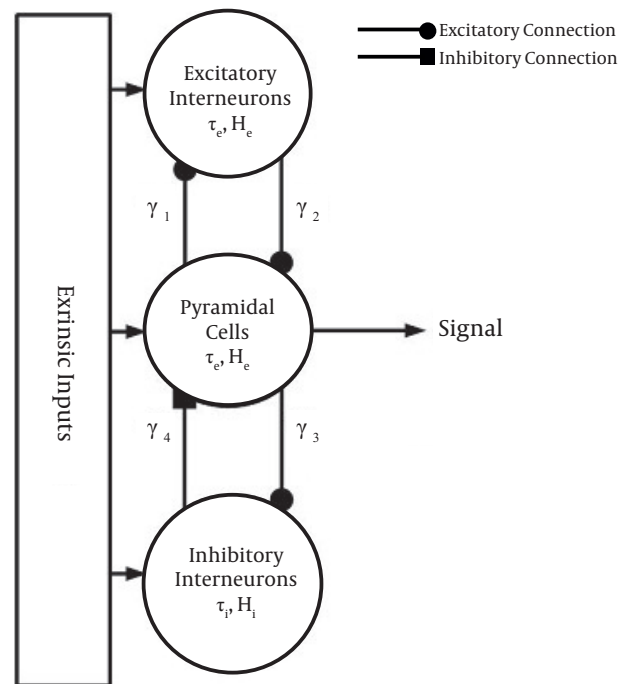


Figure 1. Jason model for a cortical area. Three subpopulations are considered to model the cortical area. Pyramidal cells have interactions with both excitatory and inhibitory interneurons.

forward and lateral connections is that in the latter the targets are pyramidal cells. Two sided and hierarchical connections are distinguished with the fact that two sided connections are completely symmetric which creates a great synchronization. One other special characteristic of the two sided connections is their ability to simulate dynamics of the same phase.

4. Results

4.1. Brain Behavior in Autism Spectrum Disorder

It seems autism spectrum disorder (ASD) is potentially caused by unbalanced portion of excitation/inhibition; in other words, a disproportionate high level of excitation (or disproportionately weak inhibition) in neural circuits mediates language and social behaviors. More excitable (more weakly inhibited) cortex is, by its nature, more poorly functionally differentiated (4, 12, 13)

This kind of cortex, with high excitation and low inhibition, leads to extended anomalies in perception, memory and cognition and even motion controllers. Moreover, noisy cortex (over-excited and differentiated functionality) is, by its nature, unstable and prone to epilepsy. Almost 38% of Autistic children suffer from epilepsy while in general population of children it is only 2% (3, 14). Unbalanced

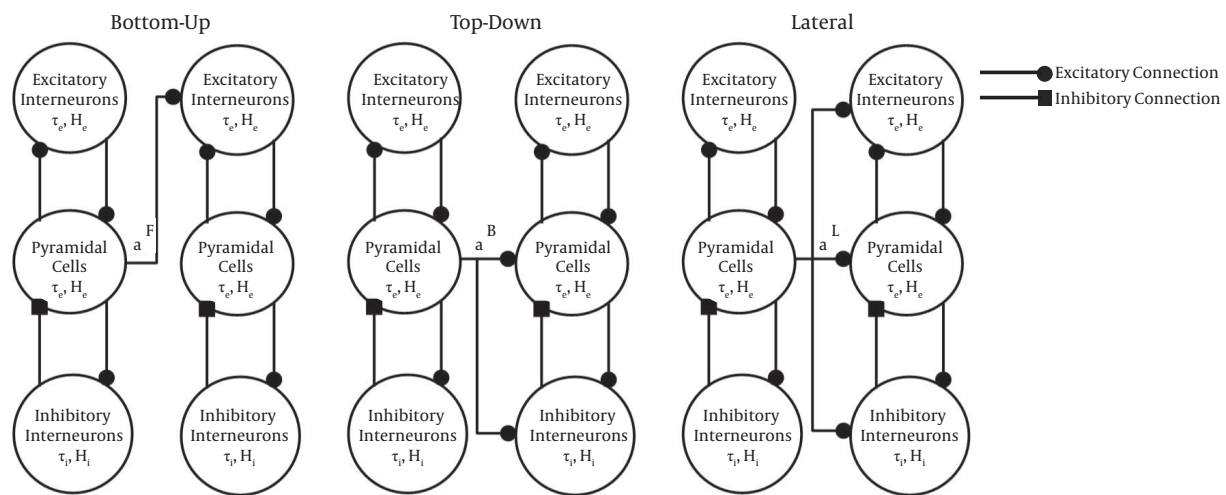


Figure 2. Hierarchical connections between Jansen units are based on simplified rules of Felleman and Van Essen. Coupling parameters control each type of connections.

proportion of excitation/inhibition can be due to increase of glutamate signal (excitation) or decrease of inhibition resulted from low GABAergic signal. Suppressed GABAergic inhibition is considered as a common factor in suspected etiologies of autism (15).

Based on this hypothesis, flaw in these neural systems is resulted from abnormal proportion of excitation/inhibition (or from another point of view is due to increase of noise in cortex and sub-cortex).

4.2. Cortical Network in ASD

Autism is a disorder in which multiple aspects of behavior, emotion, language and cognition are disrupted, among which, autistic individuals appear to have a range of perceptual processing abnormalities, expressed especially entirely by a high level of sensitivity to auditory and tactile stimuli (3, 16-18).

Molecular/circuit-based mechanisms can cause and increase brain excitation level.

In the cortex, both excitatory and inhibitory neurons receive extensive extrinsic and intrinsic inputs of glutamatergic. Pyramidal projection neurons and local-circuit spiny stellate cells in the neocortex have glutamatergic (excitatory) connections. In the cerebral cortex, roughly 80% of the neurons are excitatory glutamatergic neurons and 20% are inhibitory GABAergic neurons. It should be noted that during development, the GABAergic cortical cells are excitatory (19).

The balance between excitation and inhibition in cortex is controlled by glutamatergic activities and GABAergic neurons. Levels of activities are set by extrinsic excitatory factors (glutamatergic thalamic afferents). The com-

bination of both excitatory and inhibitory factors (serotonin, norepinephrine, dopamine and acetylcholine afferents from the hindbrain, midbrain and basal forebrain, respectively) and inhibition is inserted to the cortex. In other words, other effective factors on excitatory or inhibitory processes that are set by glia, the vasculature and the cerebrospinal fluid system, have to be taken into consideration.

5. Discussion

There are some types of cells that balance the numerical and functional evenness of excitatory and inhibitory cells, or some effects that lead to over excitation; people with this imbalanced situation are endangered and prone to epilepsy. For example, GABAergic neurons in cortex of rodents are mostly created in an excrescence of BAZAL and are transferred to an area next to cortex (20). In both parts of production and transferring GABAergic neuron cells of cortex, some of the observed defects result in a decrease in number of GABAergic neurons, and lead to over excitation of cortex (21). Inhibition in hippocampus is lowered and lateral amygdala facilitates long term excitation of synapses (22).

As mentioned earlier, it seems that the origin of autism spectrum disorder lies in imbalanced proportion of excitation/inhibition (or from another point of view, increase of noise in self-organized cortex and sub-cortex systems), which is illustrated in Figure 2, by means of unnatural increase in excitation parameters γ_1 , γ_2 and γ_4 in comparison to inhibitory parameter. In Hierarchical ASD Model,

ASD can cause a change in top-down and bottom up connections since these connections create a loop leading to system stability. When top-down connections are stronger, amped vibrations finally stabilize.

In Figure 2, the most affected parts in ASD are lateral connections. Two-sided connections which are completely symmetric become more active, and cause extra synchronization. On the other hand, due to special characteristic of the two-sided connections and their ability to simulate the same phase dynamics, they cause unnatural asymmetry in children's EEG signal.

Footnote

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