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Mini Review

Cell Migration Hypothesis of Synesthesia

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ABSTRACT

Based on the data-mining of the recent whole-exome studies of sound-color synesthesia, we propose the hypothesis, attempting to explain how rare gene variants identified in several synesthesia-specific genes function differently compared to non-synesthetes. It turned out, that several of those genes encoding integrin, myosin, chemo-repellent and axon guidance receptor, all can be implicated in directional cell migration, or chemotaxis. Two possible mechanisms to account for these findings are proposed: Excessive migration of neural progenitors to the brain cortex areas responsible for synesthetic experience; impaired recruitment of microglia to the synaptic contacts, resulting in the impaired synapse pruning and the formation of excessive contacts between the neurons responsible for synesthesia, such as the neuronal connections between visual and auditory areas of the cortex. More representative genome sequencing and cellular neurobiology studies are needed to investigate our hypothesis in greater detail.

Keywords: Cell migration; Exome sequencing; Genome sequencing; Microglia; Molecular genetics; Sequence variants; single nucleotide polymorphisms; Synaptic pruning; Synesthesia

INTRODUCTION

Synesthesia is an unusual human condition involving mixing of the senses, in which stimulation of one sensory modality triggers sensation experiences in another sensory modality [1-9]. There are various kinds of Synesthesia: Sound-color, phoneme-color and many others. The concept of Synesthesia is introduced in famous memoir by Nabokov V [7], "Speak Memory", and neuropsychology masterpiece "Mind of Mnemonist" by Luria AR [6], later, the books on this subject by Cytowic RE and Ramachandran VS [2,3,8,9]. Synesthesia has long been known to be inherited and passed in families from direct ancestors. It was thought for a while that it is X chromosome-linked condition. Candidate chromosome linkage regions were also mapped on certain autosomes [2,3]. Outstanding questions of ongoing research on molecular genetics of Synesthesia are: What are the molecular cellular signaling pathways, individual genes, single nucleotide polymorphisms and human-specific gene expression signatures implicated in various modes of Synesthesia?

Genetic variations implicated in synesthesia

In particular, it is interesting to focus on genetic variations implicated in Synesthesia. Neuroscientists following this subject of research might be aware of recent study of axon genesis genes implicated in sound-color Synesthesia by Tilot AK [10]. Below a new hypothesis in the fascinating area of research is presented, that is very intriguing, in particular, because of recent discoveries which triggered my genuine interest. This hypothesis is called "Cell Migration Hypothesis of Synesthesia". It is based on the recent published findings of the groups working in Max Planck Institute of Psycholinguistics, University of Cambridge, Dept. of Psychiatry, Autism Research Center, Daunders Institute of Cognition and Behavior, Readbout University – research groups led by Simon Baron-Cohen and Simon Fischer, investigating the rare variants in genes they implicated in sound-color (auditory-visual) Synesthesia. They studied three families of synesthetes, sharing sound-color Synesthesia: Comparing those individuals within the families who have Synesthesia, with those who don't have it. Those individuals were subjected systematically to "whole

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exome" genome sequencing and analyzed by sophisticated bioinformatics tools the most interesting genes that light up as those genes that possess unique rare variants, specifically associated with synesthetic condition. They discovered the list of 37 genes with rare variants tightly associated with synesthetic phenotypes in the studied three families. In this article authors present and analyze in terms of Gene Ontology (GO), interpret the data. Certain genes that are either known to be implicated in cell migration or those which might be hypothesized to be implicated in cell migration – also light up in this study of sound-color Synesthesia-associated gene variants. It is especially intriguing and worthy to focus on those discovered genes. One genes pair are ROBO3 (RIG1) and SLIT2. ROBO3 is "Roundabout Homologue 3". SLIT2 is "Guidance Ligand 2". They both fit to the pathways that regulate growth cone guidance and neurite outgrowth. They have been also implicated in chemotaxis and cell migration. This is really intriguing and interesting! In this couple of genes SLIT is ROBO receptor binding protein, while ROBO is a receptor. According to the authors, these two genes do not necessarily fit to the very same pathway; they might belong to parallel pathways. In any case, they are both involved in the same function, ROBO-SLIT pathway of axon guidance. This piece of data looks very interesting to me because of the known function of ROBO3 in cell migration. It is involved not only in axonal guidance, but also in chemotaxis, for example, leukocyte cell migration. SLIT2 is secreted chemo repellent, a molecule that blocks the outgrowth in certain direction; preventing processes (axons) reach certain destination. Its action is opposite to chemo-attractants, molecules that make moving cell chemotax in certain direction. It is rather over simplistic to think about ROBO/SLIT genes as being only involved in growth cone guidance. They are certainly involved in cell migration. Among 6 "hits" of this study, there are also other genes implicated in cell migration. What those genes are? One of them, ITGA2 is Integrin Alpha 2. It is a receptor for laminin and collagen. It has been shown to play a role in filopodia protrusion, which is a function relevant for cell migration. The functions executed by the integrins in cell migration are of special interest in this context. Integrins are well-known to interact with adhesion molecules, chemo-attractants, molecules that guide cell migration. They are integral plasma membrane-spanning proteins which transduce extracellular signals and triggering cell migration behavior within responding cells. Another discovered gene is a myosin, Myo 10. Myosins are actin-based motors, regulating actin filaments, actin-myosin interactions. There are many types of myosins. What is interesting about Myo 10? The finding that it binds both actin and microtubules. It also binds beta-integrin. It is well-known, thus, that myosins are also involved in regulation of cell migration. We might be not so sure whether Myo 10 is involved in regulation of cell migration. However, it is well established that another myosin homologue, Myosin 7, has closely related homologue in Dictyostelium, a classical model of cell migration. It is known to be involved in cell migration. Also Myo 10 has 3 PH domains, which bind PI P3 phospholipids. PH domains are well-known for their function of recruiting PH-domain containing proteins to plasma membrane. Very often, PH-domain containing proteins are critically involved in control of cell migration and chemotaxis-in Dictyostelium and higher eukaryotes. Therefore, Myo 10 is a good candidate to control cell migration.

Another protein, a gene variant for which was also found in this study [10], SLC9A6 (NHE6), a transporter, Proton/Na^+/K^+ exchanger is localized to axon spine and dendrites and very likely functions in axon's and dendrite's extension. This a central candidate gene found in the discussed study. Therefore, the number of gene candidates found in this study, light up in Gene Ontology, as "cell migration" genes. The authors noticed this finding and mentioned it within the article.

Cell migration hypothesis of synesthesia

Let's start now presenting a Cell Migration Hypothesis and how it might be implicated in Synesthesia. How does cell migration play a significant role in the developing brain? Two important key functions can be pointed out, that seem to be relevant: Migration of neural progenitors in neurodevelopment, and migration of microglia during synapse remodeling [1,4]. Neurodevelopment in which neurons find their positions and migrate toward certain layer within either the brain cortex or cerebellum, for example. The neuronal progenitors occupy certain position/area, such as certain layer of the cortex. To achieve this goal, they use guidance ques in a process quite different from the outgrowth of neurites and axons. The bodies of neuronal progenitors navigate in certain direction. This navigation happens in developing brain, typically, through radial glia, forming the paths, along which neuronal progenitors migrate towards their destination. This is important because such cell migratory behavior in synesthetes could be somehow different - more neuronal progenitors of certain type could be attracted to neuronal centers compared to their normal counterparts. We do not know if it is true or not because there is no neuropathology or neuro-histology evidence for synesthetes. Certainly, we can excuse ourselves for this lack of knowledge. If during the neurodevelopment concentration (aggregation) of neuronal progenitors in certain cortex areas takes place (for example, the areas of connection between auditory and visual cortex). One possibility is if there is excessive abnormal concentration of neurons in synesthetes, compared to matched normal human beings. However, there is no factual evidence for this scenario. Thus, theoretically, we can assume that there is certain difference in the numbers of neurons attracted to the areas responsible for synesthetic experience, due to the differences in locomotion of neuronal progenitors between the synesthetes and regular normal humans. Obviously, we lack any serious evidence to support this hypothesis. There is very intriguing brain imaging fMRI data-the areas active during synesthetic experience have been mapped by such studies [5]. This data is consistent with predictions, for example, for sound-color Synesthesia, that certain areas of auditory and visual cortex as well as the connections between them light up in these functional brain imaging studies [5]. Another possibility, however, looks much more realistic and attractive. Cell migratory differences point rather not to neuronal progenitors or neuroglia, but to the immune-competent cells within the central nervous system, namely-microglia [1,4]. Those cells

intrinsically display migratory behavior. Typically, microglial cells are attracted to the areas of neuro-inflammation. They are characterized by the important function-participation in remodeling of inter-neuronal contacts between the dendrites and axons. Neuronal synapses are being remodeled actively during neuro-plasticity. One of the important functions of microglia is "pruning" of neuronal connections [1,4]. Since microglia is involved in removal of excessive connections between the neurons during neurodevelopment, we can hypothesize that given that excessive connection is the basis for Synesthesia, as it was previously established, microglia could be somehow intimately involved in this process. This is when Cell Migration comes into play because, if those areas that have excessive neuron-neuron contacts responsible for synesthetic phenomena, are remodeled in a way that they still have excessive connections compared to normal human beings, in which these connections are being actively removed by active microglia, then we can assume that cell migration of microglia is affected specifically in synesthetes.

DISCUSSION

Those gene variants discussed above, therefore, might affect the ability of microglia to migrate and in turn-remodel, prune neuronal connections involved in Synesthesia. This is the basis for my idea stating that pruning of neuronal connections is a key phenomenon, under control of migrating microglia that is foundation of the difference between synesthetic and non-synesthetic individuals. In nutshell, the genes possessing rare variants in the recent studies may be hypothesized to affect the ability of microglia to migrate to the brain areas, where critical contacts between certain specific neurons are formed. Since these gene variants affect the ability of microglia to migrate, these cells are attracted to these areas and less synaptic pruning takes place in the affected brain areas. Less synaptic pruning means more excessive connections between the affected neurons-which accounts for the phenotype that is observed. More representative genome sequencing and cellular neurobiology studies are needed to investigate our hypothesis in greater detail.

CONCLUSION

Very interesting findings of this study point to such neuronal phenomena (neurite and growth cone outgrowth, axonal outgrowth and guidance), that maybe affected by the activities of those genes that have rare variants in the dataset. These exciting data fit really well to what researchers think about etiology of Synesthesia, being a condition, in which extensive connections between neurons take place. The extensive outgrowth of the processes connecting abnormally to where they should not connect, reach the areas they should not reach, make new excessive connections. Those are consistent findings and conclusions that are not questioned in any way. Nevertheless, one may notice something really fascinating and exciting-the data point to another Gene Ontology category, namely, "Cell Migration".

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CONFLICT OF INTEREST

The author does not have any conflict of interest.

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