Possible Alterations in Parvalbumin Immunopositive Interneurons in and 5 in Area 9 of the Prefrontal Cortex in Schizophrenia

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Abstract
Schizophrenia is a devastating disorder which affects approximately 1% of the population in the United States it affects roughly 2.2 million people. Research suggests that it is a neurodevelopmental disorder emerging in late adolescence to early adulthood. Previous studies have shown that the prefrontal cortex, more specifically areas 9 and 12 are affected in individuals with schizophrenia. The prefrontal cortex is important as it is involved in executive functioning. Research from our lab has shown a variety of alterations with the pyramidal cells, projection neurons in these areas. Research by Lewis et al., (2013) suggests that schizophrenia maybe caused by an imbalance of signaling between the pyramidal cells and the interneurons in the cortex. Therefore we have begun to examine two types of interneurons basket cells and chandelier cells. We hypothesize that those two populations based on their connections to the pyramidal cells will have an altered cell density in both areas 9 and 32 of the prefrontal cortex.

Introduction
Schizophrenia is known for having a large magnitude of deficits in several cognitive domains. The cognitive deficits of schizophrenia include impairments in current IQ, sustained attention, category fluency, verbal memory, response inhibition. (Lewis 1) The area of the brain that are associated with this issue is the prefrontal cortex (specifically, the dorsal lateral prefrontal cortex or DLPFC). Lower gamma oscillations that are detected from this area are some of the physical characteristics of schizophrenia. Gamma oscillations are often between the range of 32 to 80 Hz. In order for normal gamma oscillations to occur there needs to be stable interactions between several pyramidal cells and parvalbumin cells. There also needs to be a satisfactory amount of GABA and GAD to regulate feedback within the cells. During several studies with animal subjects, those with lower GABA had a lower frequency within regions of the brain and lower cognitive function. Higher amounts of GABA and GAD lead to increased gamma oscillations and stronger cognitive control. To determine the effects of lower GAD and GABA on the DLPFC we must observe the presence of cells that require or synchronize with those chemicals. Postmortem observations of several brains help us gain a hypothesis.

Methods

Control 3878
Schizophrenic 3742

Brain #

Distributive Os
Age
Sex
PMT
Layers
Area
Storage time (Months)

1671
schizophrenic
43
M
21.8
II & V
32
10

1748
Control
44
M
23
II & V
32
8

3813
schizophrenic
67
M
21.3
II & V
32
13

1878
Control
65
M
13
II & V
32
11

3742
Control
71
M
13
II & V
32
7

1875
Control
68
F
14
II & V
32
12

3915
schizophrenic
34
M
17.4
II & V
32
10

3932
Control
38
M
21.9
II & V
32
10

3546
schizophrenic
69
M
17.83
II & V
32
13

3619
Control
74
F
19.8
II & V
32
11

3557
schizophrenic
66
F
16.75
II & V
32
13

3625
Control
70
F
18.25
II & V
32
11

1634
schizophrenic
71
M
13
II & V
32
15

1626
Control
65
F
16.6
II & V
32
11

Two-tailed paired t-test p = 0.084
t= 2.015

References


Discussion
The preliminary data from the study supports the current hypothesis that schizophrenia is a result of alterations in the excitatory and inhibitory balance in the cortex. Previous data from the lab shows dramatic decreases in spine density on the pyramidal cells as well as loss of basal dendrites, and alterations in MAP2, neurogranin, and calbindin immunostaining. Our data suggests an increase in parvalbumin immunopositive cells in area 9 of the prefrontal cortex in schizophrenia. Previous research to examine cations in immunostaining which would suggest a change in expression of the protein shows an increase in immunostaining in layer IV.VI suggest an increase in production of parvalbumin possibly do to an increase in inhibitory neuron activity or increase in immunopositive cells. Parvalbumin positive cells are most abundant in layers II/III and synapse on pyramidal cells in layer III (7). There is additional evidence that layer III interneurons make long-range connections, which may explain the increase in parvalbumin immunostaining in the subcortical white matter (7). Preliminary data suggests a decrease in immunostaining in layer IV would suggest a possible decrease in parvalbumin expression and possible activity. The data taken together with previous research in the lab suggests a possible increase in inhibition of layer II pyramidal cells with a decrease in excitation on the same cells as seen by the loss of spines and dendrites on those cells. The decrease in immunostaining in layer II along with a decrease in spines and dendrites on the pyramidal cells suggest compensation for the loss excitatory synaptic surface area by decreasing parvalbumin expression. Much research suggests that this may be the case in the dorsolateral prefrontal cortex in schizophrenia. Research from the lab on an animal model for prefrontal cortical development suggest loss of thalamic input during development results in loss of spines and basilar dendrites in the dorsolateral prefrontal cortex. The loss of spines is more pronounced in layers II VI than in layer V. The data taken together is suggests that schizophrenia has its roots in development and may be related to a loss of excitatory input that leads to alterations in the excitation inhibition balance as seen in alterations in parvalbumin immunostaining, loss of spines and loss of dendrites. More research needs to be done to confirm the preliminary result.