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# Neuropathology of the Prefrontal Cortex Neuropil in Schizophrenia

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## 1. Introduction

Schizophrenia is a brain disease with a multitude of symptoms and deficits in several areas of the brain. While the search for the neuropathological mechanisms of most diseases of the brain remain a forefront in the frontier of brain research, studies in schizophrenia has progressed significantly within the last three decades; however, the central etiological mechanisms of this devastating disease remains a mystery. A new impetus was gained with the landmark study by Johnstone et al., (1976) using computed tomographic (CT) scans, reported dilation of the lateral ventricles in a small group of chronic schizophrenic patients. Following this study, numerous more sophisticated neuroimaging studies using techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, consistently showed ventricular enlargement, sulcal widening and cortical atrophy in schizophrenia (Reveley et al., 1982; Andreasen et Al., 1988, 1990, 1994; Lawrie and Abukmeil 1998; Van Horn and McManus 1992). Lateral ventricle studies showed a 20-75% increase in the ventricular to brain ratio (Daniel et al., 1991; Van Horn and McManus 1992) and a median 40% increase in volume using MRI (Lawrie and Abukmeil, 1998). Additionally, some of these volumetric studies also showed an 8% decrease in the overall temporal lobe and 4-12 % decrease in volume of medial temporal structures, such as the hippocampus, parahippocampus and amygdala (Lawrie and Abukmeil 1998). Of significant importance are imaging studies of monozygotic twins discordant for schizophrenia. In all pairs studied the affected twin had the larger ventricles (Reveley et al., 1982; Suddath et al., 1990) and smaller cortical and hippocampal size (Noga et al., 1996). These studies were supported by data from family studies, which showed that the affected relatives had larger ventricles and smaller brain volume (Honer et al., 1994; Sharma et al., 1998; Silverman et al., 1998). Buchanan et al., (1998), in an effort to identify reductions in specific subregions of the frontal lobe, found a 13% decrease in the inferior prefrontal grey matter compared with an average 5% decrease in other frontal regions. MRI studies of subcortical structures showed small decreases in the thalamic volume of schizophrenics (Andreasen et al., 1994; Buchsbaum et al., 1996; Byne et al., 1997, 2001, 2002; Jones 1997, Popken et al., 2000; Young et al., 2000; Brickman et al., 2004). Structural imaging findings and macroscopic changes in the brain provided the impetus for more stereomorphometric and immunocytochemical investigations of the cytoarchitecture of cortical and subcortical structures of post-mortem brains. One particular area of major interest has been the prefrontal cortex (PFC).

The prefrontal cortex is located in the frontal lobe. It is rostral to premotor and primary motor areas. The PFC is the prominent cortical projection of the medial dorsal (MD) nucleus of the thalamus (Takagi 1980; Yarita et al., 1980; Price et al., 1981). It also receives reciprocal connections from areas of the diencephalon, mesencephalon and limbic system as well as cortical afferents of visual, auditory and somatic origin (Barbas et al., 1989: Barbas 1992). It is one of several association areas in the brain and is concerned with cognitive behavior and motor planning. The prefrontal cortex can be divided into several subregions; however, there are two main regions: the prefrontal association cortex proper, located on the dorsolateral surface of the frontal lobes, and the orbitofrontal cortex, located on the medial and ventral portions of the frontal lobe (Leonard 1972). In primates, the mid-dorsolateral PFC is targeted as a locus for working memory processes, and it encompasses the region within and above the principal sulcus (Broadmann's areas 46 and 9). In recent years, many studies have focused on the prefrontal cortex as a site of perturbation in schizophrenia (Benes et al., 1991; Shapiro, 1993; Davis and Lewis, 1995; Perone-Bizzozero et al., 1996; Beasley et al., 1997; Glantz and Lewis, 1997; Honer et al, 1997; Garey et al., 1998; Selemon and Goldman-Rakic, 1999; Kalus et al., 2000; Buxhoeveden et al., 2000; Lewis et al., 2001; Pierri et al., 2001, 2003; Broadbelt et al., 2002, 2006, 2008; Jones et al, 2002; Kindermann et al., 2004; Kolluri et al., 2005; Vostrikov et al., 2007; Subroto et al., 2009; Somenarain et al., 2010). Functionally, the prefrontal cortex is involved with attention, memory, orderly thinking and planning (Goldberg 1995), cognitive functions which have been shown to be impaired in schizophrenia and patients with damage to the prefrontal cortex (Weinberger et al., 1988), all of which are altered in schizophrenics.

Much evidence points specifically to the dorsolateral prefrontal cortex (DLPFC) as a site for dysfunction in schizophrenia (Weinberger et al., 1986; Buchsbaum et al., 1990; Benes 1991; Pakkenberg 1993; Goldman-Rakic and Selemon 1995, 1997; Lewis 1995, 1997; Harrison 1999; Andreasen 2000; Thune et al., 2001; Jones et al., 2002; Broadbelt et al., 2002, 2006; Miguel-Hidalgo et al., 2005; Kolluri et al., 2005; Somenarain et al., 2010). Schizophrenics perform poorly on tasks that require the use of working memory (Baddeley 1986). The intricate nature of working memory was first identified in studies of human cognition (Norman 1970, Baddeley 1986). Working memory allows one to simultaneously keep several pieces of information in mind for a few short seconds. For example, a newly read phone number is stored until it is dialed and after it is immediately forgotten. Morphological post-mortem studies in the DLPFC showed an increase in neuronal density (Benes et al., 1991; Selemon et al., 1995) without a change in the number of neurons (Pakkenberg 1993; Thune et al., 2001). Both Benes et al., (1991) and Selemon et al., (1995) hypothesized that increases in neuronal density without a change in the number of neurons would imply a change in the DLPFC neuropil, which includes the axon terminals, dendrites and dendritic spines that are the site for most cortical synapses. This was corroborated by several studies that showed a decrease in the synapse-associated protein synaptophysin (Karson et al., 1996; Perrone-Bizzozero et al. 1996; Glantz and Lewis 1997). A study by Buxhoeveden et al., (2000) reported reduced neuropil space in area 9 of schizophrenics. There are consistent findings of reduced spine density in layer III pyramidal neurons of the temporal cortex, BA 22 and 38, and frontal cortex, BA 10 and 46 (Garey et al., 1993, 1998; Glantz and Lewis 2000; Kolluri et al., 2005). Understanding the significance of these alterations requires an understanding of which elements of the DLPFC circuitry are disturbed. Functional maturation of the DLPFC circuitry in monkeys and humans seems to be uniquely protracted. It does not become

functionally mature until after puberty (For a review see Lewis 1997). Human PET studies by Chugani et al., (1987) showed cerebral blood flow in the frontal cortex does not reach adult levels until 15 to 19 years of age. This seems to correspond with the appearance of clinical symptoms during late adolescence in schizophrenia. Additionally, adult levels of performance on some cognitive tasks, like delayed-response tasks, subserved by the DLPFC are not achieved until after puberty in both monkeys and humans (Fuster 1989).
Several studies have examined the morphology of pyramidal cells in the prefrontal cortex. Two studies showed a decrease in soma size and others decreased spine density (Garey et al., 1993, 1998; Glantz and Lewis 2000). Soma size is directly proportional to dendritic and axonal arborization (van Ooyan et al., 1995; van Pelt et al., 1996); therefore, a decrease in soma size, as seen in schizophrenics, might lead to decreases in dendritic arborization. The studies on spine density, Garey et al., (1998), examined the prefrontal cortex in general and not specific brain areas whereas, Glantz and Lewis (2000) examined areas 46 and 17.

## 2. Decreases in MAP2

More recently, studies by Jones and collaborators have investigated areas 9 and 32 of the prefrontal cortex (Jones et al., 2002, Broadbelt et al., 2002, 2006, 2008; Somenarain et al., 2010). These studies targeted the pyramidal cell and its ultrastructure: dendrites, spines and structural proteins. They first showed significant decreases in Microtubule Associated Protein (MAP2), a protein found in dendrites and cell bodies, in layers III and V of areas 9 and 32 of the prefrontal cortex Jones et al., (2002). Microtubule-associated proteins (MAP) are proteins that promote tubulin capacity to self-associate into microtubule polymers (Herzog and Weber 1978). Microtubule-associated proteins can also interact with actin filaments and with components of the intermediate filament proteins thus, pointing to their functional role in the regulation of the functional organization of the cytoskeletal network of neurons (For review see Maccioni and Cambiazo 1995). The family of neuronal MAPs includes high-molecular-mass components, namely MAP-1A, MAP-1B, MAP-1C, MAP-2A, and MAP-2B; the neuronal MAP-3; MAP-4 is found in both neuronal and nonneuronal cells; and intermediate-size polypeptides such as tau; and the small 70-kDa MAP-2C. MAPs have been found to be compartmentalized in neurons, with MAP1 being widely distributed, while MAP2 is essentially a dendritic protein and tau an axonal component. The majority of MAPs have a rather widespread distribution among different cell types and even tissues, but certain MAPs have been found localized in specific cells and not in others (For review see Maccioni and Cambiazo 1995).
MAP2 was first described by Murphy and Boresy (1975). It is an abundant protein in brain tissues which copolymerizes with brain microtubules in vitro and promotes the polymerization of tubulin. High levels of MAP2 can be found in the somatic and dendritic compartments, but not axons (Matus and Bernhardt 1986). In dendrites MAP2 is associated with microtubules and has an active role in the development and maintenance of dendritic processes by promoting polymerization of tubulin to form microtubules (Hirokawa et al., 1988). Because of its role in microtubule assembly and its selective association with dendrites, MAP2 has been implicated as playing a major role in the molecular mechanisms regulating dendritic growth and stabilization (Matus and Bernhardt 1986). Therefore, assembly and stability of microtubules are regulated by MAP2. MAP2 is a sensitive cross-linker and adjustable spacer in dendritic architecture. The phosphorylation state of MAP2 modulates its interaction with microtubules. In low-phosphorylation states MAP2 binds to

microtubules and increase microtubule assembly and/or stability. Increased phosphorylation decreases these effects (Audesirk et al., 1997). Hely et al., (2001) proposed a model which suggests that dephosphorylated MAP2 favors elongation by promoting microtubule polymerization and bundling; whereas, MAP2 phosphorylation which increases microtubule spacing could cause dendritic branching. This is through the action of CAMKII being activated by elevated calcium concentrations, which is regulated upstream by calmodulin and neurogranin. Dendritic branching is due to changes in the cytoskeleton through the interaction of microtubules and actin filaments. Any factor that can alter microtubule dynamics will affect the dendritic architecture. The MAP family of proteins is known to regulate many factors of microtubule dynamics such as, deploymerization, bundling, spacing, and interaction with actin filaments (for review see Maccioni and Cambiazo 1995).

## 3. Loss of dendrites and spines

The loss of MAP2 immunostaining in their first study (Jones et al., 2002) suggests a loss of dendritic material on the pyramidal cells. The second study from their lab reported decreases in the primary and secondary basilar dendrites in area 32 of the prefrontal cortex (Broadbelt et al., 2002). There are mainly two types of neurons in the cortex, pyramidal and non-pyramidal neurons. The pyramidal neurons constitute about 70% of the cortical neurons and the non-pyramidal neurons about 25% (Powell 1981). The pyramidal neurons have a pyramidal shape cell body with an apical dendrite extending towards the pial layer and several basal dendrites on the base of the cell body. These neurons are the primary cortical projection neurons and are of major interest in this regard. Their axon collaterals extend for considerable distances horizontally through the gray matter and give rise to clusters of axon terminals in the superficial layers, which are organized as a series of stripes 2 μm wide and 1.8 mm long (Levitt et al 1993). There are reciprocal connections among these stripes and over 90% of the synapses furnished by these collaterals target the dendritic spines of other pyramidal cells (Metchitzky et al., 1995). It was suggested that these connections could provide the substrate for reverberating cortical circuit that coordinates and maintains the activity of spatially segregated, but functionally-related populations of DLPFC pyramidal neurons during the delay phase of the delayed-response task (Lewis and Anderson 1995).

The dendrites have tiny projections called spines which are the sites for synaptic inputs to the neuron. Spines are protrusions of the neuronal membrane consisting of a head connected to the neuron by a thin spine neck. They can be found on the dendrites, the soma and on the axon hillock (Mates and Lund 1983). Spines are the site of synaptic transmission and about 90% of the synapses on spines are excitatory (Mates and Lund 1983). There are three types of spines: mushroom, stubby and filopodium. Spine density is a marker of the number of excitatory inputs to pyramidal neurons (Mates and Lund 1983). Glutamate and dopamine afferents terminate on dendritic spines whereas, GABA terminals are often found on dendritic shafts and cell bodies (Levitt et al., 1993). Moreover, several hypotheses implicate one or more of these neurotransmitter systems in the pathophysiology of schizophrenia (Weickert et al., 1998; Haroutunian et al., 2003; Bergson et al., 2003). Somenarain 2005, have observed a decrease in spine density in both Layer III and V in Area 9. Layer III pyramidal neurons are the corticocortical projections (Lund et al., 1975); they play a critical role in information processing such as working memory. Layer V pyramidal

neurons are the main projection cells from the cortex to other subcortical and cortical areas (Lewis 1997); therefore, changes in information in one cortical area could affect many brain regions. Additionally, a loss of spines reflects a loss of excitatory input to these neurons; therefore, it is expected that cognitive information processing might be disturbed as seen in schizophrenia. This is consistent with previous reports of decrease synaptophysin, a 38-kd integral membrane protein of small synaptic vesicles, which is important in calcium-dependent synaptic transmission (Glantz and Lewis 1997). Moreover, the spines of basal dendrites receive both dopamine and glutamate afferents (Smiley et al., 1992); thus, this give credence to possible disturbances in these transmitter systems in schizophrenia. Additionally, the basal dendrites are the site for afferents from the MD nucleus of the thalamus, an area of the brain that has consistently shown neuroanatomical deficits in schizophrenia (Andreasen et al., 1994; Buchsbaum et al., 1996; Byne et al., 1997, 2001, 2002; Jones 1997, Popken et al., 2000; Young et al., 2000).

## 4. Decreases in neurogranin

Recently, studies from the Jones group have reported significant decreases in neurogranin, a protein found in dendrites and spines (Broadbelt et al., 2006; Somenarain, 2005). Neurogranin (RC3), a postsynaptic calpacitin, was first identified in a hybridization study designed to isolate mRNAs enriched in the rat forebrain but absent in the cerebellum. As the name indicated, it was rat cortex-enriched cDNA clone number 3 (Watson et al., 1990). Neurogranin was independently purified by Baudier et al., (1991) from brain based on its affinity for calmodulin (CaM) and as a substrate for protein kinase C (PKC). Neurogranin is only 78 amino acids long and has sequence similarity to neuromodulin, a protein associated with axonal growth cone development and maturation (Baudier et al., 1991). Interestingly, both neurogranin and neuromodulin share a 20 amino acid sequence, AAAAKIQASFRGHMARKKIK, designated as the IQ motif (Apel and Storm 1992). This sequence contains a binding domain for CaM and a PKC phosphorylation site (Baudier et al., 1991). Neurogranin however, is found abundantly in neuronal cell bodies, dendrites and dendritic spines. In areas such as the frontal parietal cortex, granular cells of the dentate gyrus, apical dendrites of pyramidal cells of the CA1 and CA3 regions of the hippocampus, and the striatal cortex (Chicurel et al., 1993, Neuner-Jehle et al., 1996). Immunoelectron microscopic studies in the cerebral cortex, hippocampus and neostriatum in rats showed that neurogranin exists in the perinuclear and dendritic cytosol. It concentrates in dendritic spines in close proximity with postsynaptic densities and subsynaptic membranes (Watson et al 1992, Neuner-Jehle et al., 1996). This position is quite interesting, because neurogranin is a PKC substrate that interacts with CaM and both PKC and CaM are required for the induction of long term potentiation (Gerendasy and Sutcliffe 1997). Much research suggest that neurogranin might be involved in $Ca^{2+}$/CaM and PKC-dependent cascades that guide dendritic spine development and remodeling, as well as long-term potentiation (LTP) and long-term depression (LTD). Neurogranin binds calmodulin and, therefore, renders it unable to interact with free calcium (Ho et al, 2000; Prichard et al, 1999). Knockout mice lacking neurogranin exhibit problems with spatial learning and long-term potentiation (Ho et al, 2000); suggesting a role for neurogranin in processing and transmission of information and suggesting a possible role in schizophrenia. Gerendasy and Sutcliffe (1997) postulated that neurogranin regulate $Ca^{2+}$ fluxes in dendritic spines by releasing CaM to bind $Ca^{2+}$. The size and duration of $Ca^{2+}$ fluxes determine which $Ca^{2+}$-dependent enzymes are stimulated

and ultimately, which second messenger cascades are activated for LTP or LTD. Enzymes such as CaM kinase II and adenylate clyclase favours LTP; whereas, calcineurin and cyclic nucleotide phosphodiesterase, favors LTD (For review see Gerendasy and Sutcliffe 1997). The binding of calmodulin by neurogranin is abrogated by phosphorylation by PKC, oxidation by nitric oxide or large concentration of $Ca^{2+}$ (Ho Pak et al., 2000 and Prichard et al., 1999). Most recently, a study by Broadbelt et al., 2008 showed a decrease in calmodulin in the prefrontal cortex suggesting that the calcium calmodulin dependent pathway may be altered in the PFC.

Immunohistochemical studies in rats and mice showed that peak expression of the neurogranin protein postnatally coincides with developmental periods of rapid dendritic growth and the formation of 80% of cortical synapses (Alvarez-Bolado et al., 1996, Uylings et al., 1990). Suggesting therefore, an increase in neurogranin concentration coincides with the onset of synaptogenesis. The number and size of spines on dendrites is mediate by calcium-dependent mechanisms that are initiated by glutamate receptor-mediated influx of $Ca^{++}$ ions (Gerendasy and Sutcliffe 1997). Proteins involved in $Ca^{++}$ signaling, such as neurogranin, therefore may play a major role in spine morphology and number and as such cell signaling.

A loss of neurogranin is suggestive of both morphological and functional alterations in the prefrontal cortical area 9. Much evidence has pointed to morphological changes in the pyramidal cells in the prefrontal cortex. Recent data have shown functional alterations in these cells as well. This data represent the first link between morphological alterations and functional alterations in pyramidal cells in the prefrontal cortex. Future work needs clarify the significance of these alterations and how they contribute to the behavioral and cognitive problems observed in patients with schizophrenia.

## 5. The role of antipsychotic drugs

Since their introduction in 1959, neuroleptic drugs have been used extensively in the treatment of schizophrenia and other neuropsychiatric diseases, such as bipolar disease, depression and schizoaffective disease (Harrison et al., 2000). Most of the patients in recent neuropathological studies in schizophrenia have received neuroleptic medication. In recent years a battery of treatments have become available that treat the symptoms of schizophrenia and attempt to improve the quality of life of patients. The conventional or older typical antipsychotic medication (phentothiazines, butyrophenones, and thioxanthenes) e.g., chlorpromazine, haloperidol, fluphenazine and molindone are used to reduce the positive symptoms of schizophrenia and have a strong affinity for dopamine and serotonin receptors (Hirsch and Weinberger 2003).

The recently developed medications e.g., clozapine, risperidone, olanzapine, quetiapine and sertindole are more effective against the negative symptoms of schizophrenia (Hirsch and Weinberger 2003). The newer medications, often called atypical because they have a different mechanism of action than the older medications, are more effective against negative symptoms and show fewer side effects, and are effective against treatment-resistant patients. The therapeutic effects of the major neuroleptics, typical or atypical, are based on their ability to bind neurotransmitter receptors like dopamine and serotonin (Harrison 1999a). There are five classes of dopamine receptors $D_1$-$D_5$; all are seven transmembrane domain G protein-coupled receptors linked to adenyl cyclase (Harrison 1999a). The serotonin 5-HT receptors are divided in seven branches 5-$HT_{1-7}$. The 5-$HT_3$ is an

ion channel and all the others are coupled to G protein linked to adenyl cyclase or the phosphor-inositol system. The 5-$HT_{2a}$ is of particular relevance in schizophrenia because of it affinity for atypical neuroleptics (Harrison 1999a). Though, $D_2$ blockade has been central to the antipsychotic activity of typical neuroleptics. The atypical neuroleptics such as clozapine bind to $D_1$, D3, $D_4$ and $D_5$ as well as 5-$HT_{2a}$ and noradrenergic receptors; however, $D_4$ shows the strongest affinity (Harrison 1999a). Recently, the dopamine $D_4$ and 5-$HT_{2a}$ receptors are of particular importance in schizophrenia due to their binding mechanisms with atypical neuroleptics. The exact mechanisms of how these interactions operate are still under investigation.

Although they are treasured for their therapeutic significance, neuroleptics are known to produce structural brain changes in areas such as the striatum, where there are increases in the number of symmetric and axodendritic synapses relative to asymmetric and axospinous synapses (Benes et al., 1985, Klinzova et al., 1989, Meshul et al., 1992). Suggesting that antipsychotics induce an altered numerical balance in favor of inhibitory synapses, given that asymmetric and axospinous synapses are mostly glutamatergic and as such excitatory (Benes et al., 1985). Some reports suggest a correlation of antipsychotic dosage and increase brain atrophy and decrease thalamic volume (Gur et al., 1998). These macroscopic studies suggest that neuroleptic exposure is a potential confounding variable in most morphological and neurochemical findings reported in schizophrenia. Several studies have suggested that long-term treatment with antipsychotics might cause the morphological changes observed in schizophrenia (Benes et al., 1985; Klinzova et al., 1989; Meshul et al., 1992). Although these studies were done in rodents with normal brains, together the data provide good evidence that chronic antipsychotic treatment induces synaptic plasticity and alters the synaptic ultrastructure.

A study on rhesus monkeys demonstrated long-term haloperidol exposure can increase phosphorylation of MAP2 and down regulate spinophilin, a dendritic spine associated protein (Lidow et al., 2001). A study in rat showed treatment with antipsychotics can modulate the expression of MAP2 genes (Law et al., 2004). This is different from what is shown for MAP2 in schizophrenia (Somenarain et al., 2010); therefore, animal studies may not be the best indicator of neuroleptic effect. Additionally, animal studies are based on normal neural networks so the neuroleptic drugs may not have the same effect as altered neural networks. Because antipsychotic drugs can affect many neurotransmitter systems (Harrison et al., 2000), they have the ability to regulate the activity of kinases and phosphatases via second messengers (Lidow et al., 2001). These enzymes regulate phosphorylation states of many proteins, one such is MAP2 (Diaz-Nido et al., 1990). MAP2 is found in dendrites and cell bodies and is an important protein in formation and stabilization of microtubules (Matus 1988). Phosphorylation of MAP2 can destabilize dendritic microtubules because it is a sensitive cross-linker and adjustable spacer in the polymerization of tubulin in microtubules, and as such the cytoskeletal processes of the cell (Boyne et al., 1995).

In order to correctly interpret the morphological data it is important to know what alterations are due to neuroleptics and which are not. A comparison of drug-naïve and treated subjects in contemporary postmortem studies is not feasible since nearly all patients with schizophrenia use neuroleptics. The use of animals to study the effects of antipsychotics has some attraction; however, there are problems when extrapolating results between species. First, the cerebral cortex in animals and humans vary in terms of size and the distribution of neurotransmitter receptors. For example, rodent's cerebrum is a thousand

times smaller than humans (Harrison et al., 2000). Secondly, there are marked differences in organization of the PFC. For example, in primate PFC there is a distinct layer IV which is absent in rat (Harrison et al., 2000). Lastly, rodents metabolize antipsychotics differently than humans, and might respond neuropathologically in different ways; moreover, animal brains are normal (Harrison et al., 2000).

Thus, researchers have devised other means to control for neuroleptic exposure. The use of a non-schizophrenic group treated with antipsychotics, such as bipolar disease, schizoaffective and depression often produced mixed results (Harrison et al., 2000). This is attributed to the fact that a significant number of patients who were first diagnosed as schizoaffective or for depression are later diagnosed with schizophrenia, which suggest that they share intrinsic pathological features with schizophrenia (Harrison et al., 2000). Therefore, it is foreseeable why when used as controls for neuroleptic exposure the results are overlapping. Somenarain (2005, 2010) have used a cohort of Huntington Chorea brains to determine if neuroleptic drugs can cause morphological changes in the brain and confound the results reported in schizophrenia. Although there are reports of cortical changes in Huntington Chorea (Harrison et al., 2000), the main deficit is a loss of neurons in the striatum (Harrison et al., 2000). Huntington's patients experience some psychiatric symptoms, like hallucinations and delusions, similarly to schizophrenics; therefore, many are given neuroleptic drugs to control those symptoms. A comparison of schizophrenic and Huntington Chorea is a more meaningful assessment in determining if neuroleptic drugs could be responsible for some of the morphological changes reported in schizophrenia. Somenarain (2005) have done an exhaustive study comparing MAP2, Neurogranin, dendrites and spines in schizophrenia, Huntington Chorea and normal controls. All of the above parameters were shown to be decreased in schizophrenia; however, there were no significant differences seen between Huntington Chorea and controls. We believe that this is strong support that neuroleptic drugs may not be responsible for some of the changes seen in DLPFC neuropil in schizophrenia.

## 6. Conclusion

The loss of dendritic material on the pyramidal cells in the DLPFC may have an indelible impact on the functional capacity of these neurons. These neurons are the primary cortical as well as subcortical projection neurons; therefore, they play a very important role in information processing. Functionally, the DLPFC is involved in attention, memory, orderly thinking and planning, functions that have been shown to be disturbed in schizophrenia. The loss of MAP2 may have a detrimental impact on the structural integrity of neurons. MAP2 proteins play a very important role in the regulation of the functional organization of the cytoskeletal network of neurons. The loss of this protein supports the studies that showed loss of dendrites and spines. Whether the loss of MAP2 is the cause or as a result is not known. The loss of neurogranin provides additional support that there is a loss of dendritic material on the pyramidal cells of the DLPFC. Neurogranin postnatally coincides with developmental periods of rapid dendritic growth and the formation of cortical synapses. The loss of neurogranin is suggestive of both morphological and functional alterations in the prefrontal cortex. There is strong support that the losses of these substances is real and are probably not due to neuroleptic exposure. This is supported by the fact that Somenarain (2005) did an extensive study using Huntington chorea brains which showed no changes due to neuroleptic exposure compared to controls. Together,

these studies provide very strong support that the DLPFC neuropil is reduced in schizophrenia.

## 7. References

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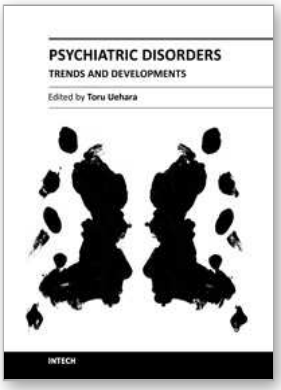


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Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, sever and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.



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