# The Potential Role of Giftedness in the Evolutionary Perpetuation of Schizophrenia

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# ABSTRACT

Timothy Crow‟s evolutionary theory of schizophrenia has received a great deal of attention since its incarnation in the 1990s (Crow, 1990); the theory postulates schizophrenia to be a form a developmental delay resulting from deficient lateralization of function, at least “for some key aspects of language” (1990). However, since rates of schizophrenic psychopathology hold stable (WHO, 1967), Crow himself acknowledges the theory is thus limited by the absence of a potential balancing factor to account for the retention of the cortical symmetry he believes automatically generates symptomatology (Crow, 1997); research has of yet been unable to identify such a factor. Consequently, this manuscript attempts to shift Crow‟s framework by positing cortical symmetry as not in itself pathological, but merely as an alternative form of human brain organization, with degrees of functionality ranging from giftedness to schizophrenia. Evidence for this, as well as for the varying factors that may contribute to distinguishing between the varying forms of phenotypic presentation for Crow‟s „symmetry gene‟ are discussed in depth, so as to construct an etiological model of the potential probability of schizophrenic incidence amongst this subgroup.

## RÉSUMÉ

La théorie évolutive de la schizophrénie émise par Timothy Crow a reçu énormément d‟attention depuis son incarnation dans les années 90. Par contre, vu que le taux de psychopathologie schizophrénique reste stable, Crow reconnaît lui-même que la théorie est limitée par l‟absence d‟un éventuel facteur d‟équilibre, pour rendre compte de la rétention de la symétrie corticale qu‟il pose comme générant automatiquement la symptomatologie. Les recherches jusqu‟à présent n‟ont pourtant pu identifier un facteur approprié. Conséquemment, ce manuscrit est une tentative de déplacement du cadre d‟analyse de Crow à un cadre dans lequel la symétrie corticale est posée comme n‟étant pas pathologique en soi, mais comme étant une forme alternative de l‟organisation du cerveau humain – avec des degrés de fonctionnement allant d‟un niveau élevé de surdoué à la pathologie schizophrénique. Les preuves à l‟appui, et celles à l‟appui des différents facteurs qui pourraient contribuer à une distinction entre les différentes présentations phénotypiques du „gène de symétrie‟ de Crow, sont discutées de manière approfondie, pour construire un modèle étiologique de l‟éventuelle probabilité d‟incidence de schizophrénie parmi ce sous-groupe de la population.

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Though named for the literal translation of the Greek „split mind", recent schizophrenia research suggests the opposite; with advances in neuroimaging techniques, evidence now points to the disease being one of increasing cortical symmetry in comparison to the laterality of the population at large (Petty, 1999; McDonald et al., 2000; Kwon et al., 1999). Of chief interest is not only the consistency in reduced anatomical asymmetry in sufferers, but also the lack of hemispheric specialization of functions typical of controls (Berlim, Mattevi, Belmonte-de-Abreau & Crow, 2003). Consequently, a belief is emerging that schizophrenia may represent a developmental delay in which the patient has failed to establish hemispheric dominance, at the very least for "some key aspects of language" (Berlim et al., 2003).

Curiously, however, beginning with the World Health Organization"s (WHO) 1972 *Ten Country Study of Incidence*, there have been consistent reports of stability in the rates of „core symptoms" of schizophrenia over time and across varying populations (Jablensky et al., 1992; WHO, 1972). Consequently, this implies causality extending beyond environmental factors, which vary widely throughout generations and across cultural and geographical divides

(Berlim et al., 2003). However, if not for the exclusive culpability of nurture, where does the induction of psychopathology begin?

It is within these limitations that Oxford University‟s Dr. Timothy Crow has proposed a promising evolutionary theory of schizophrenia, suggesting the involvement of a single sex-linked gene – which he believes to be responsible for reduced hemispheric differentiation – in the predisposition for psychosis (Crow, 1990). Unfortunately his framework, as he readily admits, is fundamentally hindered by a lack of an identifiable compensatory mechanism through which to explain the survival of the „symmetry gene‟ (Berlim et al., 2003).

Furthermore, it is my position that Dr. Crow may have been too hasty in his assumption that disruptions in interconnectivity, and subsequent cortical development, follow *directly* from a lack of achieving hemispheric dominance for function. Consequently, in this manuscript, I will attempt to demonstrate that the bilateral trait has survived evolutionary pressures for the very same reason that it hinders; in other words, schizophrenia may be due to the fallout of a potential great strength: that of cortical symmetry itself. As such, my hope is that through an

elucidation of Dr. Crow‟s insight, and its comparison to research on symmetrical individuals as a whole, I will be able to construct a model in which bilaterality emerges as a distinct form of cortical organization with varying phenotypic presentations – only some of which contribute to symptomatology, while others prove advantageous. In other words, I aim to propose that schizophrenia may not result directly from bilaterality per se, but from disruption to the atypical synaptic connectivity patterns characteristic of a healthy bilateral brain.

However, in constructing this model one need consider other, non-psychotic groups of adults who present with the „symmetry gene.‟ Also, the various factors that differentiate the degrees of synaptic retention belonging to the gene‟s various phenotypic presentations must be addressed, as I believe the extent of synaptic retention is crucial to distinguishing schizophrenics from healthy *bilateral* individuals. Consequently, this paper will progress in four parts: 1) the first will give the history and background of Dr. Crow‟s theory, sketch the proposal for symmetry as more than mere pathology, compare schizophrenics to other bilateral individuals, and explicate what I believe to be the unique importance for superior myelination capacity in

symmetrical cortical patterning, 2) the second will consider factors in utero which may contribute to the possibility of symptom presentation for symmetrical individuals, 3) the third integrates Dr. Allan Schore‟s developmental theory of „attachment and the right brain‟ and considers its consequences in lieu of symmetrical brain organization, 4) the fourth and final section investigates factors in adulthood that I believe could either facilitate or guard against psychotic symptom presentation in bilateral individuals. These are followed by a concluding section, in which the findings from the previous divisions of the manuscript are integrated and the consequences for future research in the field are discussed.

However, first it is appropriate to consider briefly my unusual methodological approach.

## METHODOLOGY

As this is a theoretical manuscript with partitions, each of the four divisions contains its own individual review of the literature in the form of an introduction, a results section in the form of a comparative literary analysis, and a discussion section, in which the consequences of the literary history and its recombination are laid out. The results sections, or

products of the literary analyses, are the meat of the body of each of the four divisions of the paper, which are followed by discussion sections in which the findings are progressively analyzed. As this organizational style is somewhat unusual, the sections are clearly demarked and listed in the table of contents for ease of reference.

This thesis should be viewed as constructing an etiological model sequentially throughout the human life span up until the point of typical symptom presentation (which generally occurs in the early to mid-twentieth year of life in schizophrenia). Consequently, each section progressively discusses and integrates previously addressed findings, so as to attempt to build an integrated model of the various factors contributing to schizophrenic symptom presentation.

With this, I turn to Dr. Crow‟s theory.

## RESULTS AND DISCUSSION

### Division I: Evolutionary Psychobiology and Schizophrenia

#### *Why an Evolutionary Theory?*

The universality of the schizophrenic diagnosis, as demonstrated by the World Health Organization‟s survey (WHO, 1967), is not the only indication of genetic

interference in the disorder. The lack of identification of a common environmental influence that differs in comparison to controls (Berlim et al, 2003), as well as the reality that illness onset in siblings occurs at the same *age* rather than time (Crow, 1986), both point, along with a series of other factors, to an involvement of genetics in the disease (Berlim et al., 2003). However, seeing as schizophrenia is associated with a reduction in fecundity (approximately 30% in females, and 70% in males) (Berlim et al., 2003), if a genetic factor is involved, what prevents its elimination via sexual selection from the gene pool?

Seeing as “the incidence rate of „core schizophrenia‟ (roughly 1% of human populations) exceeds a mere chance effect due to high mutation rates” (Brune, 2004), most believe that for this reason evolution dictates that a balancing advantage must be present, in either heterozygous carriers of the gene or in healthy individuals possessing it, in order for deleterious affects to have been avoided (Berlim et al., 2003). Early contenders considered for the compensatory role included mechanisms outside of the nervous system, and, consequently, both lower than average incidence of infection, and higher than average

fertility rates were found in first-degree relatives of schizophrenic patients (Brune, 2004).

However, studies upholding these positions have been criticized for failing to control for schizoid personality traits, comorbidities, and other factors that would likely interfere with results; even more troubling, they do not account for the consideration that incidence of the disease does not vary across populations as the risk of infection, or incidence of fertility, fluctuates (Brune, 2004). Taken together, these concerns have contributed to an emerging consensus amongst academics in the field, who are now in agreement that the probability of a genuine link between schizophrenic etiology and either of these factors is minimal (Brune, 2004). Similar results have been prevalent across varying attempts at uncovering a corporeal balancing factor, and, as such, researchers have shifted focus to the nervous system in the search for the compensatory mechanism at work in the selective sustenance of psychotic psychopathology in the human gene pool (Brune, 2004).

*Dr. Crow's Proposition*

Consequently, in the research three findings consistently differentiating schizophrenics from controls

became of particular interest, being: 1) reduced cortical mass, 2) ventricular enlargement, and 3) reductions, absences or reversals of typical functional and anatomical asymmetries (Berlim et al, 2003). Furthermore, the particularly high incidence rates of premorbid language disorders in afflicted individuals (Rosen, 1996), combined with the lack of pronounced lateralization for language functions, and the consistent incidence rates across all populations, led Dr. Crow and colleagues to contemplate that schizophrenia emerged at the time of the speciation event, before the migration of humans from Africa (Crow, 1997). The subsequent theory proposes that a mutation on the highly variable region of homology caused the asymmetry characteristic of the prototypical human brain, and as such, allowed for the development of the complex language structure present in hominids, but not in the great apes (Crow, 1997).

This theory centers on the assumption that *intra*hemispheric specialization of functions (such as that of the dominant language functions of the left hemisphere, and the visuospatial functions of the right hemisphere) presented an advantage to the individual inheriting the asymmetrical gene, as the time constraints of

*inter*hemispheric communication through the corpus callosum (25 ms) were avoided “if the neural apparatus necessary to perform each time critical task is gathered in one hemisphere” (Crow, 1997). Consequently, the theory proposes that reduced communication times allowed for the development of more complex speech, and that the resulting increased language capabilities enhanced the desirability, and hence the sexual selection of males exhibiting this gene by females; as a result, prevalence of the trait increased, causing it to become synonymous with our species (Crow, 1997).

In support of this proposition are studies implying the presence of the gene responsible for the relative growth of each of the two hemispheres‟ on the X chromosome (Berlim et al, 2003), as well as the potential lack of recombination between the X and Y chromosomes at the region of homology, which may, in part, contribute to the sex differences in handedness, symptomatology and age of onset of the disease (Berlim et al., 2003). A further discussion of the rationalization behind the potential location of the gene is outside of the scope of this paper; however, the evidence to support its location is profound (Berlim et al., 2003).

Consequently, within this framework, schizophrenia is viewed as a developmental delay, in which reductions in brain mass and enlargements in ventricular size are seen as a result of a failure to achieve hemispheric dominance due to a less evolved „symmetry gene‟ (Crow, 1997). Crow and colleagues support the proposition that “symmetrical development of the cerebral cortex (itself) implies a smaller, and perhaps less convoluted cortex” (Berlim et al., 2003), and they bolster this claim through reference to lower premorbid intelligence and reduced cortical mass in schizophrenic patients (Crow, 1997).

*However*, nowhere in the literature is causality established between bilaterality and reduced cortical mass, and furthermore, no gene has as of yet been identified that conclusively differentiates schizophrenics from the general population (Berlim et al., 2003). In addition, the presence of asymmetry in the cortices of other species, including left hemispheric sound production in songbirds (Nottohm, 1976), and right hemispheric visual navigation in rats (Sherman, Garbanati, Rosen, Yutzey & Denenberg, 1980), indicates that asymmetry has, in fact, existed long before the human speciation event. Therefore, I believe a further investigation

into human symmetrical brains as a whole is necessary before any solid conclusions can be drawn.

*Compensatory Mechanisms*

Perhaps the largest flaw to Crow"s theory is the circularity of his argument – if asymmetry provides a genetic *advantage*, why has its selection seemingly plateaued? Why have the rates of schizophrenia not decreased in all, or at least some populations? In other words – we are still missing a significant universal balancing factor.

In the research, it has always been ***assumed*** that one need *compensate* for bilaterality, but it is my proposal that the balancing advantage may directly be linked to the nature of symmetry itself. What if the gene for symmetrical brains was not eliminated because, on the whole, it presented an advantage? As such, in considering this proposition, we must turn to an investigation of the *typical* bilateral individual.

*The Bilateral Advantage.*

The theory that symmetry ***directly*** results in a developmental *delay* stumbles when faced with the fact that studies of cross-sections of human cortices show that

symmetrical brains, on average, are in fact ***larger*** than their asymmetrical counterparts (Rosen, 1996). In fact, it is *asymmetry* that has been shown to result from a „*failure to develop the small side*," or the early developing right hemisphere in most individuals, as symmetrical brains, on average, show two cortices equivalent to the *dominant* cortex in lateralized controls (Rosen, 1996). This is a far cry from the reduced cortical mass in schizophrenic patients, as it seems that despite this seemingly anatomically disadvantaged group, the *majority* of individuals who lack lateralization must obtain an advantage in order for symmetrical brains, on the whole, to be larger. But what can be said of functionality?

It is at this point that I would like to draw comparisons to a highly functional group, who, coincidentally, are also characterized by a lack of asymmetry of function – the extremely gifted (Singh & O"Boyle, 2004). While so called „normally gifted" individuals (IQ of 130-145), on average, display overemphasized lateralization, a reversal has been found to occur in subjects with an IQ score above 145, after which, in neuroimaging studies, the majority of individuals display *bilaterality* of most functions, ranging from language to visuospatial tasks (Singh & O"Boyle, 2004).

Consequently if, in fact, Crow is correct in assuming that a single gene can differentiate those with cortical asymmetry from those without, it is not a far cry to consider the possibility that both types of individuals – schizophrenics and their gifted counterparts – might represent two very different presentations of one specific genotype. It is within this comparison that a whole new framework of questions begins to emerge. If the potential for giftedness proves to be the balancing factor for schizophrenia, what is it that differentiates these groups from each other? And perhaps even more interestingly, what differentiates them both from symmetrical individuals who fall somewhere in between?

*There may be something else at play: Interconnectivity theory*

I believe the answer may involve the selective sustenance via myelination of certain synaptic interconnections between neurons, as investigations into the functional patterns of high-level giftedness have shown *qualitative* differences in cortical organization in comparison to average individuals (Singh & O"Boyle, 2004). For instance, in a study by Singh and O"Boyle (2004), gifted

adolescents showed a speed advantage without a loss of accuracy in the processing of tasks that involved hemispheric *cooperation* versus those that were unilateral, a reversal from the pattern of controls, demonstrating that these individuals not only experienced enhanced *inter*hemispheric communication, but also were characterized by an atypical pattern of symmetrical synaptic connections (Singh & O"Boyle, 2004). These findings are strengthened by studies that indicate left-handedness, which is associated with bilaterization, correlates highly with an increase in the number, and a decrease in the speed, of connections in the corpus callosum (Driesen & Raz, 1995). An increase in *inter*hemispheric connectivity is thus assumed to characterize the symmetrical brain.

A secondary attribute of these individuals is their improved tendency for immediately localizing appropriate cortical areas for specific brain functions (Singh & O"Boyle, 2004). For instance, in a visual task for identifying the emotionality of chimeric faces, an EEG study demonstrated that highly gifted adults quickly exhibited a shift in electrical activity exclusively to the specific locations necessary for judgments concerning the emotionality of a face, whereas average adults shifted randomly for a significant period, and

never fully settled on the proper locals (O'Boyle, Alexander & Benbow, 1991). In further EEG studies, this lack of ambiguity in the gifted has been shown to result from an *increased* ability to selectively inhibit regions *not* necessary for task performance (O'Boyle, Alexander & Benbow, 1991; O'Boyle, Benbow & Alexander, 1995). It is hypothesized that this enhanced *inhibitory* ability may serve to insulate the gifted brain from the disruptive *inter*hemispheric "cross talk" that would otherwise occur as a result of increased callosal function, and distract the individual from the task at hand (Singh & O'Boyle, 2004).

Conversely, studies have shown that the "aetiology of schizophrenia has been repetitively linked to a *dysfunctional* intra- and interhemispheric connectivity" (Brune, 2004). Therefore, it is not surprising that sufferers are characterized by reductions in the size and number of connections in the corpus callosum (Berlim et al., 2003).

Furthermore, in terms of symptomatology, schizophrenics are characterized by distractibility and difficulties with attention, both of which are characteristic of a lack of *inhibitory* synaptic connections. As such, it is plausible that a disruption in *inhibitory* pathways in schizophrenic patients could result in a reduced ability to

*limit* electrical activity to the required cortical areas for task performance, therefore contributing to the non-relevant inter- and intrahemispheric chatter that is thought to underlie positive symptoms.

Consequently, it seems that this disorder may not be a *direct* result of bilaterality, but rather represents a disruption in the development of healthy symmetrical brain organization, which, though not pathological in itself, still *qualitatively* differs from the typical patterning of asymmetrical controls. As such, Crow may be correct in classifying schizophrenia as a developmental delay found only in symmetrical individuals, though one may not follow directly and automatically from the other. Instead, it is my proposal that schizophrenia could be conceived of as a form of developmental delay resulting not from asymmetry itself, but which manifests itself only in a susceptible healthy subset of the populace – those with qualitatively atypical, though typically healthy, asymmetrical brain organization. However, if this *is* the case, what can be seen to cause these disruptions in the synaptic development of schizophrenic individuals?

*Discussion*

For an answer to this question, I believe we must turn to developmental neurophysiology, which has established that during cell elaboration, spanning the third trimester of pregnancy through the first few years of life, all humans produce as many as 100% more synapses then will eventually exist in their adult states (Vasta, Haith & Miller, 1999). The sustenance of connections depends on the extent of their maturation, which is dictated by both use, and the respective ease of myelination that follows (Vasta et al., 1999). In other words, supplemental myelination leads to increased probability of synaptic retention. Furthermore, the difference between one individual and another in the speed at which a synaptic connection is myelinated – following the same amount of use – is determined by genetics (Vasta et al., 1999).

However, the extent to which each interconnection is used in early life may be influenced both by innate patterns of preferred processing – such as the inter-/intra-hemispheric processing biases of symmetrical and asymmetrical individuals, respectively – and by the presentation of environmental stimuli that encourage the practice of particular patterns of use (Schore, 2001a). As

such, both the *extent* of synaptic connectivity and the *particular dominant patterns* retained in any adult brain are partially influenced by both the nature and nurture of that individual. Consequently, the possibility exists that both genetic and environmental influences may affect the disruption in connectivity that underlies the presentation of schizophrenia.

Based on the aforementioned evidence for a divergent pattern of synaptic connections in the bilateral brain, it seems likely that a gene coding for cortical symmetry may be closely linked, or itself dictate, an atypical innately preferred dominant pattern of use. This may, in the presence of optimal early environments, prove to be a superior pattern of connectivity, therefore leading to an intellectual *advantage* in the typical symmetrical individual over their asymmetrical counterparts.

Nevertheless, it is also probable that a second, unassociated gene codes for ease of myelination, and thus establishes an individual‟s limitations regarding their potential range of overall synaptic retention. If such an inferior „myelination gene‟ were to coexist with the „symmetry gene‟ in one individual, it is possible that both

together could result in schizophrenic symptom presentation.

As such, while symmetrical individuals possessing an *enhanced* myelination gene may have an *increased* probability of giftedness due to their potentially *advantageous* dominant interconnectivity patterns, those *lacking* an enhanced myelination gene may be susceptible to a unique form of developmental delay – one in which the degradation of the tenuous *inter*hemispheric dominant synaptic patterning may contribute to the symptomatology present in schizophrenia (for an illustration of this relationship, please see the Appendix below). This hypothesis is supported by the fact that myelination continues throughout the lifespan, but experiences a sharp drop following puberty (Vasta, Haith & Miller, 1999). As such, disruption in *this* ability may partially explain the lack of symptom presentation in schizophrenic patients until early adulthood.

In addition, research has established that a range of environmental factors can also positively or negatively affect synaptic connections (Schore, 2001a). As such, environment may play a significant role in the potential presentation of psychosis, regardless of which genotype may exist for ease

of myelination, as environment dictates opportunity for synaptic use in the first three critical years of life, the period during which synapses are still developing (Vasta, Haith & Miller, 1999). Consequently, the more synapses created, the more available for future maturation via myelination, and thus the more retained. It is important to note here that this period overlaps the time frame for the formation of attachment patterns in humans (Schore, 2001a), and, consequently, I will pay heed to an earlier stream of research and contemplate whether attachment relationships may affect psychosis via altering the patterns and extents of synaptic interconnectivity in ways which may be particularly disruptive to symmetrical brain organization (Schore, 2001a).

It seems possible that the significant variability in symptom presentation associated with schizophrenia could be due, in part, to varying causes, and therefore varying patterns, of improper synaptic development. For instance, the *extent* of both reduced interhemispheric and inhibitory connectivity in the schizophrenic brain may vary in extent to each other, resulting in distinctive symptom presentations. This convergent hypothesis reflects evidence that there may be multiple methods via which to disrupt the development of

a symmetrical individual, and thus to contribute to the presentation of psychopathology.

From here, it is not difficult to assume that bilateral individuals may be characterized by increased sensitivity to a number of factors, which may, in part, reflect their relative lack of abundance in the human gene pool despite their proposed potential for intellectual advantages. However, a number of factors point to a recent increase in the presentation of cortical symmetry, at least in the populations of industrialized countries. For instance, the incidence of left-handedness (McManus, 2002), autoimmune diseases (Lemke & Lange, 2002), allergies (Ehrlich & Chiaramonte, 2003), and myopia (Lambert, 2002), have all witnessed an escalation in presentation over time, all of which are associated with bilaterality and enhanced right hemisphere development (Benbow, 1986), and all of which correlate positively with high level giftedness (Benbow, 1986). Left-handedness and an increase in the immune response have also been associated with schizophrenia, most likely due to their linkage to symmetrical brain structure (Firestone & Marshall, 2003).

However, despite indications that bilaterality is on the rise, the rates of schizophrenia have remained stable over

time; I propose that this may actually represent a *decrease* in the presentation of the disease, as there has been a reduction in the incidence of symptoms in comparison to the size of the *susceptible* population.

It is possible that this may be partially attributed to either or both a reduction in the presentation of the proposed gene for inferior myelination, and/or an increase in the quality and variety of environmental stimuli presented to infants during synaptic development. Consequently, we may see a rebound in schizophrenic presentation in adults exposed to significant deteriorations in environment that span the second trimester through the third year of their early life; this proposition is supported by evidence of increased incidence of the disease in individuals who themselves, or whose mothers, were exposed to war during this critical period (Boog, 2004).

These assumptions tie back into Dr. Crow‟s theory for the purpose of the preferential selection of laterality. It is possible, as Dr. Crow proposed, that in order to bypass the 25 ms communication time between the cortices, the presentation of a mutation on the region of homology that allowed for cortical asymmetry was enhanced through sexual selection. However, it is also possible that following

this enhancement, but before the symmetrical gene was completely eliminated from the human gene pool, a second mutation occurred in a separate „myelination gene," allowing for the possibility of an increased speed of interconnectivity across the corpus callosum that paralleled, or was superior to, intrahemispheric communications in the asymmetrical brain. This may indicate that increased connectivity, though always advantageous, preferentially enhances symmetrical brains, leading to the recent increase in the sexual selection of bilaterality.

In fact, it is this pattern that is evidenced in the cortices of the extremely gifted, who show superior processing times for all tasks, but, as mentioned above, even greater enhancement in those that require the *cooperation* of the two hemispheres (Singh & O"Boyle, 2004). In fact, these individuals are characterized by superior interhemispheric processing times in comparison to intrahemispheric, a reversal from the patterns of lateralized adults, further supporting this hypothesis (Singh & O"Boyle, 2004). The increase in corpus callosum size and extent of myelination in bilateral brains may also be seen as supportive (Driesen & Raz, 1995).

If these assumptions reflect reality, they would explain the slow growth in incidence in cortical symmetry over time as the existence of the inferior myelination gene decreases and environmental desirability increases. In other words, as the factors that led to the enhanced *susceptibility* of the symmetrical brain decrease, it becomes increasingly free to exhibit its organizational *advantage* on intelligence, and thus to become favored in the evolutionary process. These factors may account for the low penetrance of symptomatology in the first-degree relatives of schizophrenics, as well as the above average creativity in these same individuals (Firestone & Marshall, 2003). Consequent to the latter, they may explain the surprisingly low correlations between the IQs of affected individuals in comparison to their healthy siblings (Firestone & Marshall, 2003).

Furthermore, the potential affects of the environment may contribute to the preservation of intellectual ability found in a small subgroup of schizophrenic patients, as though the vast majority are premorbidly impaired, advanced intellectual abilities have been found in others, such as in renowned physicist John Nash (Badcock, Dragovic, Waters & Jablensky, 2005). This may be due to a reduction in only

certain synapses in a minority of patients, a trend that might demonstrate that though increased myelination may reduce the probability of schizophrenia in symmetrical individuals, it does not eliminate the risk.

*Conclusion*

Through these arguments, I hope to have established my purpose of expressing a need for a shift in schizophrenic research towards a focus on the interplay between two potentially separate factors - non-hemispheric dominance and synaptic connectivity - in the development of the disease. I believe that it is only via investigation into the functioning of the average bilateral individual, that the implications of symmetrical cortical growth may be understood. Consequently, if Crow"s genetic predisposition holds true, schizophrenia may begin to be seen as a disorder affecting only a certain subset of individuals.

Given the aforementioned, we should not neglect the possibility that the lack of conclusive factors for the differentiation of sufferers from controls may be due, at least in part, to the fact that we have been asking the wrong questions. It appears likely that the existence of cortical symmetry in individuals outside of the schizophrenic

population could account for the failure of science to identify further genetic or environmental influences on the disease, as thus far studies have focused on differentiating afflicted individuals from the population at large, which may be confounded by the presence of non-affected bilaterals in the control groups.

Therefore, I propose that we abandon attempts to isolate characteristics „specific" or „unique" to the schizophrenic individual, and instead begin to conceptualize this disorder as the developmental fallout of a certain type of fully functioning human. As such, research questions should not focus on what genetic or environmental influences differ in affected individuals in comparison to their lateralized counterparts, as these factors may selectively affect symmetrical brains differently. Instead, future studies should stress the importance of proper controls, which, for the schizophrenic, must only be other cortically symmetrical individuals.

Having defined the predominant characteristics of the symmetrical brain, the crux of this research relies upon subsequent investigation into the environmental and additional genetic influences that contribute to the development of both schizophrenic and gifted individuals.

The latter being outside of the scope of this paper, I will begin to outline the making of cortical symmetry in utero via reference to the characteristic obstetric scenarios that enhance the probability of either schizophrenia or giftedness. Finally, I will turn to attachment theory to investigate the role of early experiences on later brain development, as well as to an assessment of the exacerbating or buffering affects of later occurring life events, such as significant life stress (SLS) and new attachment relationships, in the development of the disorder. It is my belief that it is only through this sort of interdisciplinary approach that we will begin to conceptualize the etiology of this convoluted disease.

## Division II: Environment in Utero

Though not the only cause of schizophrenic vulnerability, nature may very well determine symptom presentation and outcome. This claim is well supported by the existence of different disease patterns worldwide. For instance, though incidence is comparable, schizophrenics in developing countries have been characterized by less severe forms of the disorder (i.e. a reduction in the disorganized subtype), as well as by better rates of recovery

(Firestone & Marshall, 2003). It is hypothesized that this may be due to the collectivist nature of these societies, as well as to reduced stigmatization of the mentally ill (Firestone & Marshall, 2003). In addition, pressures on psychotic patients to return to work in the developing world may lead to elevated levels of self-efficacy and mastery, as well as to increases in synapse use. Consequently, both may slow the progressive synaptic pruning characteristic of the disease, the first via reductions in levels of anxiety induced nervous system-damaging hormones (Schore, 2001a), and the second through increases in myelination which, though slowed after the critical period, continues throughout an individual‟s life (Vasta, Haith & Miller, 1999). However, despite the establishment of the influence of environment, a debate still exists as to when its affects begin.

As a radioactive labeling study has shown that genetics dictate cortical symmetry during the differentiation of neurons from stem cells (Rosen, 1996), which occurs at 10-26 weeks gestation (Vasta, Haith & Miller, 1999), it seems likely that it is from this point onward that the interplay between biology and environment takes place. Consequently, the earliest experiences that may affect later

development occur in utero. Therefore, an investigation into the aspects of fetal environments that are conducive or harmful to synaptic growth may assist us in our attempt to identify factors distinguishing gifted individuals from their schizophrenic counterparts. For this reason, both enhancing and potentially damaging affects will be reviewed, in addition to one neutral, but potent factor in symmetrical development - elevated testosterone in utero.

*Enhancing Development*

Enthusiastic, „yuppie" parents have long since followed the advice of numerous studies indicating the benefits of music on fetal development (Lecanuet, Granier-Deferre & Busnel, 1988). The mechanism behind this strange phenomenon is that complex patterns of vibrations increase the stress response in the fetus, which is proposed to underlie the most basic form of learning – habituation (Leader, Baillie & Martin, 1982). This is connected to the fact that the factor most consistently correlated to high IQ throughout the lifespan is an interest in novelty present from birth (Vasta, Haith & Miller, 1999). Studies have shown that babies who demonstrate an affinity for new as compared to familiar stimuli tend to perform superiorly on later IQ tests

as a result of faster habituation following a short period of intense focus (Schore, 2001a). This focus, resulting from the selective inhibition previously discussed, is thought to increase the speed of processing; as such, infants who acclimatize to novelty faster are thought to be taking information in more rapidly (Vasta, Haith & Miller, 1999).

Interestingly, exposure to novelty has been found to create an imbalance in the homeostasis of the autonomic nervous system through an induction of the stress response (Schore, 2001a). At mild levels, this shift produces a metabolic surge in the brain, increasing its plasticity, and subsequently the probability for new synaptic connections to form and be strengthened via myelination, which, in turn, allows for homeostasis to be reestablished (Schore, 2001a). Consequently, the greater the affinity for novelty, the greater the approach behavior towards potential learning scenarios, and thus the more excitatory and inhibitory synaptic connections created in the brain (Schore, 2001a).

Therefore, in the third trimester, when synapses begin to form, the exposure of the fetus to music serves as a form of novelty, inducing a mild stress response and hence increasing the number of interconnections in the fetal brain (Leader, Baillie & Martin, 1982); this will later cause faster

habituation to novel stimuli, and increased tolerance to stress in the developed adult, both of which are associated with approach behavior towards challenges and novelty, and consequently with higher IQ (Schore, 2001a; Vasta, Haith & Miller, 1999). This affect, however, is not limited to music, but is instead produced through the exposure of a fetus, or a young child, to differing stimuli; as such, the greater the variety in stimulation a child is exposed to beginning in utero, the greater their intellectual development, and thus their probability of high synaptic retention resulting in giftedness rather than schizophrenia should their innate cortical organization be symmetrical (Schore, 2001a). The positive affects of this sort of enriched, variety filled environment is evident in studies of adoptive children, who, on average have highly advantageous early stimulation, and who, subsequently develop above average IQs (mean = 120) regardless of biological predisposition (Vasta, Haith & Miller, 1999).

*Testosterone*

Similarly, another theory that is widely held contends that elevated levels of exposure to testosterone in utero may enhance the subsequent development of the right

hemisphere, contributing to cortical symmetry. This approach, touted in the early work of Geschwind and Galaburda (1985), proposes that high doses of the steroid slow the development of the left hemisphere, while allowing for the rapid growth of the right, qualitatively altering cerebral organization, and thus contributing to left handedness, autoimmune disorders, myopia, and giftedness.

The concept that early testosterone exposure enhances cortical development is supported in a study by Shors and Miesegaes (2002), in which adult rats demonstrated increased learning capacity in times of stress if exposed to testosterone in utero, with reductions in performance following the same stressor in its absence. The theory also postulates there to be an optimal level of exposure, however, with excessive amounts of the hormone creating damage and being linked with schizophrenia (Geshwind & Galaburda, 1985). Furthermore, it is believed that slight excesses, which may overly hinder the left-brain, contribute to the disproportionate rates of language related learning disabilities in high-level gifted students (Geschwind & Galaburda, 1985).

*Negative Fetal Environments*

Conversely, research demonstrates that a range of obstetric complications (OCs) may lead to a decrease in the initial number of synapses formed, and consequently, may contribute to vulnerability to schizophrenia in symmetrical individuals later in life (Boog, 2004). For instance, a higher than average rate of preterm births were found in sufferers as compared to controls in some studies (Boog, 2004), an association that is not surprising given the declining later IQ (Isaacs et al. 2004), and increased thought disorganization characteristic of preterm infants (Vasta, Haith & Miller, 1999). Furthermore, exposure to teratogens in utero, including viral infection in the second trimester (Boog, 2004; Sham et al., 1992), as well as various others (Boog, 2004), was associated with an increased risk of later psychotic symptom development. It is assumed that this is due to reduced oxygen flow to the fetus during exposure, resulting in neuronal death. This theory is supported by evidence that caesarian deliveries due to apoxic fetal distress also result in above average incidence of schizophrenia (Boog, 2004).

The implications of in utero affects strengthen the possibility that this disorder may represent a developmental delay in symmetrical individuals equivalent to that of mild

mental retardation in lateralized brains, which is also associated with increased ventricular size and reduced cortical mass, though asymmetry remains intact (May et al., 2001). Both correlate with the same mild obstetric complications, and each lies on a continuum of severity associated with these factors (May et al., 2001). Consequently, the diversity between these two disorders may provide insight into the differences in organization between bilateral and lateralized brains, as hindrances to both seemingly result in very different symptomatology, implying differing weaknesses.

*Discussion*

Though correlations were significant in a number of studies, others have failed to find links between OCs and incidence (Mino, Oshima, Tsuda & Okagami, 2000). However, it is important to note that in utero environments may play only a small role in the development of the disorder, and are probably more representative of a factor that increases potential risk in the symmetrical individual, rather than one that is *necessary* for symptomatology. Furthermore, it is possible that the effects of both negative and positive environments would become more pronounced

if schizophrenics and the highly gifted were matched with bilateral controls in future studies. However, the affects of experience on psychosis most probably largely occurs following birth, and, as such, from here our attention turns to postnatal environmental influences, beginning with the formation of attachment relationships in the first three years of life.

## Division III: Attachment

In 1998, a single article in *Science* made waves by claiming that mothers could "invest extra energy in their young to promote larger brains" (Gibbons, 1996). This poignant depiction of the interface between neurobiology and the psychology of attachment demonstrates a growing trend in interdisciplinary research, in which external stimulation is now considered critical to the actual development and maturation of brain tissue (Schore, 2001a). This effect, mediated through the competitive selection of synapses, has been demonstrated in studies in which the natural selection of connections in the limbic system reflected the environment of an individual in infancy (Tucker, 1992). As the limbic system and associated cortical areas, which underlie the stress response, undergo a critical

period of rapid growth from the third trimester through 18 months of life (Schore, 2001a), synaptic selection in these areas directly overlaps with the formation of attachment bonds (Schore, 2001a). Therefore, it seems likely that disruptions in the fundamental relationship between infant and caregiver may negatively impact the neurobiology of these areas of the nervous system, and thus contribute to the insecure-disorganized/ disoriented behavior characteristic of Main and Solomon"s (1986) "type D," severely attachment-impaired infants; a claim that is reflected in John Bowlby"s assertions of the implications of early attachment on later mental health (1969).

Having already reviewed the effects of novel stimuli presentation, one element dictated by the primary relationship, my focus now turns to various other aspects of the attachment bond that might be implicated in these developmental disruptions. Specifically, we will focus on the evolution of play, relational recovery, and touch, all characteristic of healthy attachment, and their potential subsequent impact in contributing to either schizophrenia or giftedness in bilateral individuals.

*The Initiation of Play*

All evidence points to the existence of a milestone of normal development occurring at approximate 8 weeks of life, at which time two fMRI studies show rapid metabolic changes in the primary visual cortex denoting a critical period of synaptic growth modifiable by experience (Yamada et al., 1997 & 2000). Consequently, at this time, behavior analyses have demonstrated a shift in the child"s focus towards a preference for the caregiver"s face, especially eyes, followed by its tracking in space (Schore, 2001a). This phenomenon creates the potential for a "potent interpersonal channel" to develop (Schore, 2001a), through which the primary caregiver may tune into an infant"s cues to engage and disengage in eye contact (Feldman, Greenbaum & Yirmiya, 1999), the result of which is the initiation of the earliest form of play, in which caregiver and infant join in mutual gaze, look away, and then reestablish eye contact (Fogel & Branco, 1997), while exhibiting intense smiling and mimicking of each other"s facial expressiveness (Fogel & Branco, 1997). This reciprocal facial signaling serves as a form of imprinting, teaching the child outward expression of internal affective states (Schore, 2001a), a process that is hindered in the emotional flattening of

schizophrenia (Firestone & Marshall, 2003), and which may provide us with our first insight into the link between attachment and the development of symptomatology, as a lack of early play may contribute to negative symptom presentation later in life.

Through this process, the primary regulates the infant‟s levels of arousal (Schore, 2001a), as the presence of his or her face during periods of intense mutual gaze initiates positive “affective bursts” (Schore, 1994), characterized by dopamine (DA) release governed by the orbitofrontal cortex via the excitatory limbic circuit (Schore, 1994). Subsequently, elevated levels of DA lead to a metabolic surge in the nervous system (Schore, 1994), increased brain plasticity (Schore, 2001a), and subsequent synaptic growth that denotes learning and may contribute to the enhancement of IQ. Consequently, frequent episodes of engagement may assist in the development of giftedness via this mechanism and its additional facilitation of a sense of safety in the child, the latter of which leads to the subsequent encouragement of approach behavior towards novel stimuli (Shore, 1994), and the development of faster active „relational‟ coping strategies to reestablish positive emotional states following stress (Tronick, 1989). This

seems plausible, as both skills are encouraged through the reinforcing effects of dopamine release in positive past experiences (Robbins & Everitt, 1996), and both contribute to faster habituation rates to novelty, leading to a quicker cycling through the homeostatic imbalance necessary for mastery discussed in the previous section, and hence contributing to intellectual growth.

However, it is also crucial that the caregiver keep overstimulation at bay by allowing for periods of quiet recovery during disengagement, as the lack thereof could potentially lead to hyperarousal (Schore, 2001b), and subsequent synaptic and neuronal death via oxidative stress (Schore, 2001b). This is due to the fact that the beneficial affects of dopamine on the nervous system operate in an inverted “U” pattern (Schore, 2001a); namely, where levels of too little DA receptor stimulation reduce the possibility of synaptic growth, and excessive levels become neurotoxic, thus contributing to both the degeneration of connectivity (Filloux & Townsend, 1993), and an exacerbation of the natural process neuronal apoptosis (Filloux & Townsend, 1993). This is particularly true of the orbitofrontal cortex, which represents the “hierarchical apex of the limbic system” (Schore, 2001a), and, perhaps consequently,

enlarged and more deeply innervated orbitofrontal cortices were found in the highly gifted (Singh & O‟Boyle, 2004), while significant decreases in both were exhibited by sufferers of schizophrenia (Thimble, 1990).

Furthermore, an individual‟s lifelong narrow or broad optimal dopamine range in the orbitofrontal region is set up during this critical period, and is thus significantly affected by play interactions (Schore, 2001a). Consequently, a child who has experienced greater DA triggered positive emotional highs, following by reduced levels in quiet recovery, will form a tolerance to periods of high dopamine exposure (Schore, 2001a). This is significant, as DA is released both in response to positive and negative experiences (Schore, 2001b), and as such, tolerance development is associated with an increased ability to function optimally without synaptic degeneration later in life in a variety of environmental situations (Schore, 1991a). In other words, these individuals will be better able to respond to varying levels of DA in their system without the same severity of affects as those found in individuals whose “inverted U” DA tolerance might be narrower (Schore, 2001a). Consequently, the hypersensitivity of the D2 receptor in schizophrenic patients may be symptomatic of

few experiences of positive “affective bursts” early on (Firestone & Marshall, 2003), which subsequently may set these individuals up for increased susceptibility to synaptic pruning and neuronal apoptosis throughout the course of their entire life, possibly contributing to the reduced cortical mass found in these individuals.

*Restoration of Responsiveness*

However, sustenance of this interactive state is exhausting for the primary, who cannot maintain play indefinitely. Consequently, it is inevitable that the caregiver will not always be receptive, and as such, the stress response will be induced in the infant during periods of misattunement (Schore, 1994; Beebe & Lachmann, 1994). This leads to the learning of the regulatory pattern of “disruption and repair” characteristic of „relational“ or „interactive“ active coping (Beebe & Lachmann, 1994), in which the primary caregiver“s reattunement and comforting allows the child to return to a positive emotional state, thereby releasing dopamine, and quickly reestablishing homeostasis in the face of stress (Tronick, 1989). Furthermore, this reexperiencing of a positive following a negative experience teaches a child that “negativity can be

endured and conquered" (Schore, 2001a); therefore, physiological and conscious resilience to stress for life emerges from these processes (Schore, 2001a).

Consequently, a pattern is established that reenacts throughout the course of a securely attached individual"s life, in which curiosity is spurred by the knowledge that homeostasis can be easily attained in the event of encountered stress by returning to any stable attachment relationship and experiencing positive affect (Schore, 2001a). This increased curiosity, supported by a sense of security, contributes to greater exposure to learning experiences, leading to more synaptic connections, and subsequently resulting in higher IQ and reduced vulnerability to schizophrenia in symmetrical individuals.

The use of this system contributes to the maturation of the inhibitory limbic circuit, also governed by the orbitofrontal cortex, and responsible for regulating noradrenergic (NE) neurons in the brain (Schore, 1994). As such, this system comprises a key component of the parasympathetic nervous system that serves to inhibit the potential for poor behavior before its occurrence through a reduction of negative affect (Baxter, Parker, Lindner, Izquierdo & Murray, 2000), and the facilitation of passive

coping strategies and avoidance (Schore, 1994). Stimulation of this circuit is thus said to be behavior-calming (Arnsten, Steere & Hunt, 1996), and its optimal stimulation levels are, similar to the excitatory dopaminergic pathway, representative by an inverted “U” (Schore, 2001a), in which too little leads to excessive experiencing of neurotoxic negative affect, and too much may increase withdrawal, and therefore impede learning and subsequent IQ.

Conversely, it may not be surprising that low levels of noradrenaline are found in the brains of schizophrenics (Firestone & Marshall, 2003), as this would contribute to an inability to reduce negative emotional states, resulting in neurotoxicity, and subsequent synapse and cell death (Schore, 2001b). Seeing as the extent of an individual‟s NE tolerance is set up during these periods of “interactive repair” (Schore, 2001a), it can therefore be assumed that infant neglect may increase the vulnerability of symmetrical individuals to the disorder, a finding that is supported by correlational studies indicating a positive association between inconsistent parenting, including periods of neglect, and schizophrenia (Firestone & Marshall, 2003). The low NE levels may contribute to reduced behavioral

inhibition in these individuals, manifesting as positive symptoms later in life.

*Touch*

Finally, the last route contemplated that mediates between physiological health and the attachment bond is the experience of touch. As the primary somatosensory cortex is metabolically active at birth (Chugani, 1996), the experience of skin-to-skin contact comes online early and results in the infant actively seeking to adhere to as much skin surface on the primary caregiver as possible (Harlow, 1958). Consequently, as the tactile areas of the right hemisphere are deeply connected to the ANS (Schore, 2001a), the experience of touch begins to serve as a regulator for homeostasis, inhibiting the stress response directly. Furthermore, intimate contact is reinforced via the activation of opiate systems (Kalin, Shelton & Lynn, 1995), in which elevated levels of beta endorphins are released (Kalin et al., 1999), enhancing the pleasure experienced in the brain, and thus serving as an alternate method to reestablish positive affect following stress. In addition, opioids enhance play behavior through their tendency to increase the firing of dopaminergic neurons (Schore, 1994), further perpetuating

the stress recovery cycle. As such, physical contact may buffer vulnerability to schizophrenia in vulnerable symmetrical individuals through these three methods of reducing neurotoxicity.

Furthermore, neurobiological research indicates that the maintenance of critical levels of tactile input of specific quality and emotional content are necessary for normal brain maturation (Martin, Spicer, Lewis, Gluck & Cork, 1991). In fact, this may be especially true of the orbitofrontal cortex, as studies demonstrate that infants raised in Romanian orphanages, where they receive little to no touch, exhibit a “black hole” where this structure should be (Vasta, Haith & Miller, 1999). This finding is especially significant considering the implication of this region as a differentiating factor between giftedness and schizophrenia, with higher than average development being present in the former, and the reverse pattern being exhibited by the latter (Singh & O"Boyle, 2004 ;Thimble, 1990). As such, a child"s exposure to physical contact during the critical period of orbitofrontal development (10 – 18 months) must fall onto a continuum, in which the less frequently the bilateral infant is lovingly handled, the greater its susceptibility to developing psychotic symptomatology later in life.

*Discussion*

Altogether, this information serves to demonstrate how early attachment experiences "have longstanding and complex effects on a range of neurochemicals relevant to emotion regulation" (Coplan et al., 1998), and as such, on synaptic development and mental health. However, how might optimal and subpar primary relationships in infancy selectively affect symmetrical brains both differently and seemingly more acutely? An answer to this question may found in EEG studies, which demonstrate greater simulation of the right hemisphere (RH) during attachment behavior (Ryan Kuhl & Deci, 1997), indicating that it is both dominant for interpersonal behaviors, and consequently *most vulnerable* to them through early learning experience (Schore, 2001a). Furthermore, the increased interconnectivity between the RH and both the limbic system and the regions of the ANS that mediate the stress response (Schore, 1994), implies that individuals with greater reliance on this "earlier maturing" right hemisphere will be more affected by a disruption in its formation. As such, we must appreciate the distinctive implications the attachment bond might have for symmetrical individuals, who may be

particularly vulnerable to attachment related disruptions predominating in their increasingly used RH.

In addition, it is possible that the longer axons in interhemispheric interconnections in the corpus callosum are more susceptible to damage by neurotoxicity, possibly due to their larger surface area, and thus the greater opportunity for disruption to their function. Consequently, as these connections appear vital in the differently organized symmetrical brain, their damage would selectively affect bilaterals more extensively than they would an asymmetrical individual. Furthermore, the damage especially exhibited in the right orbitofrontal cortex, caused by disruption to any of the aforementioned three attachment mechanisms, may especially contribute to the disturbances in inhibitory synapses previously characterized as being associated with schizophrenia, as it is this area that regulates the lower order limbic systems and ANS via top down inhibition (Levin & Routh, 1996). Consequently, right orbitofrontal damage in the symmetrical cortex may contribute to the inter- and intrahemispheric chatter experienced as positive symptoms in psychosis.

For these reasons, it is easy to visualize how negative attachment relationships may contribute to a greater extent

of disruption to crucial synapses in symmetrical brains, and hence how they may contribute significantly towards the vulnerability of the potentially gifted bilateral brain towards schizophrenia. However, the patterns for the thresholds of neurochemical release and tolerance affect an individual throughout the course of his or her entire life, and as such, our investigation must now turn to how mature life events may exacerbate this damage in later life stages, contributing to the likelihood of an individual to present with the disease.

## Division IV: The Effects of Later Life Experience

Largely beginning with the work of Feinberg (1982), the research community has long since considered the role of disrupted synaptic pruning in the development of schizophrenia. Curiously, theories have abounded, naming both excessive and a lack of synaptic reduction as being associated with the disease (Keshavan, Anderson & Pettegrew, 1994). Recently, however, it has become apparent that psychotic symptoms may be linked, at least in part, to both - with key inhibitory connections being lost, while superfluous excitatory ones are retained (Keshavan et al., 1994). The concept contends that this could underlie inter- and intrahemispheric chatter and hyperarousal (Singh

& O"Boyle, 2004; Schore, 2001b), which would result in the presentation of positive symptoms, as well as in neurotoxicity, cell death and reduced cortical mass, as found in schizophrenic patients (Firestone & Marshall, 2003). Furthermore, recent studies have increasingly implicated the orbitofrontal cortex as the region most affected in sufferers, however this trend seems not to manifest itself until after adolescence (Keshavan, Anderson & Pettegrew, 1994).

This may, in part, explain why the onset of the disorder does not typically occur in either sex until early adulthood (Firestone & Marshall, 2003). As such, an investigation into the potential influences acting upon an individual at this stage that might lead to the induction or exacerbation of schizophrenic symptoms seems sensible. It is possible that either genetic or environmental factors may cause disruptions at this time (Schore, 2001a). However, the first being outside of the scope of this paper, my focus will shift to an overview of the role of stress in the presentation of syptomatology, followed by a brief investigation into each of three particular stressors – expressed emotion, social status, and trauma – in the disease. Finally, I will follow this with a discussion on how the response to adversity, and

subsequent damage, may be enhanced in the presence of insecure attachment, before presenting the potential buffering affects that later relationships and sex hormones may have on both the induction and progression of the disease.

### *The Role of Significant Life Stress*

#### *An overview.*

Though studies have demonstrated that unsettling events often precede onset, the role of stress in the perpetuation of schizophrenia is even more striking (Norman & Malla, 1993). Research has found that even minor troubles in the preceding months can be positively correlated to the presentation of symptoms; a finding that is especially striking for hallucinations and delusions (Norman & Malla, 1993). However, varying stressors seem to affect patients differently, and as such, a brief overview of three types seems key to our understanding of the links between stress and the disorder.

#### *Expressed emotion.*

Though early claims implying that schizophrenia resulted exclusively from a cold, rejecting

„schizophrenogenic" mother have been discounted, studies have shown expression of high levels of negative affect and communication disruptions are both correlated with increasing risk of psychosis amongst individuals possessing a genetic predisposition to the disorder (Cannon, Barr & Mednick, 1991). Findings such as these led Brown, Carstairs and Topping to propose that a display of attitudes and behaviors, including hostility, criticism and over-involvement by relatives, may exacerbate the condition of individuals with schizophrenia (1958). High levels of these factors, which they dubbed expressed emotion (EE), have been found to increase the risk of symptom recurrence in sufferers (Cole & Kazarian, 1993; Kazarian, 1992).

In fact, following hospitalization, those who were not on medication were six times more likely to relapse if they were in high EE (>35 hours/week) environments as opposed to low ones, as 92% of the former, but only 15% of the latter groups re-experienced symptoms in the nine months following treatment (Kazarian, 1992). Furthermore, it has been found that interventions such as family education and social skills training, aimed at reducing EE, have been successful in preventing relapse (Hogarty t al., 1986), demonstrating that interpersonal variables play a key role in

reducing the stress response and subsequent damage related to schizophrenia long after attachment disruptions in infancy.

*Social status.*

In addition, studies demonstrating that affected individuals are three times as likely to come from the lowest socioeconomic class than from any other (Hollingshead & Redlich, 1958), have led researchers to the belief that lower social status could factor into the development of the disorder. It is hypothesized that the poorer education, increased stigmatization, and fewer opportunities presented to this group could result in an increase in daily stress levels for these individuals (Firestone & Marshall, 2003), which, subsequently, could heighten their physiological arousal, and result in neurotoxicity, causing symptoms in the event of preexisting cortical symmetry (Schore, 2001b).

*Trauma.*

However, as significant as both of the aforementioned may be, there is little to no doubt of the stress induction experienced by victims of trauma, and thus it is not surprising that research has also shown a link between this

factor and schizophrenia (Resnick, Bond & Mueser, 2003). In one study, 73% of the patient sample had experienced at least one significant episode, as defined by the DSM-IV, throughout the course of their lifetime (Resnick et al., 2003), while yet another demonstrated high rates of comorbidity with posttraumatic stress disorder (Mueser, Rosenberg, Goodman & Trumbetta, 2002). Furthermore, it has been suggested that the fist psychotic episode in itself may be considered traumatic (Jackson, Knott, Skeate & Birchwood, 2004), and, as such, can lead to excessive levels of stress hormones due to a lack of coping strategies, resulting in neurotoxicity. This finding, implicating heightened responsivity in response to stress, is supported by an fMRI study in which schizophrenic patients, as compared to controls, showed significantly greater activation, particularly of the prefrontal regions of the cortex, while simply listening to trauma-related terms (Flashman et al., 2003). However, if this is the case, what causes this exacerbation?

*Discussion*

*Response to stress in the event of insecure attachment.*

This question can only be addressed by returning to the notion that many of the patterns that are established in primary attachment relationships in infancy carry over into adulthood (Schore, 2001a), and as such, poor attachment histories interact with the experiences of stress to exponentially enhance its negative affects later in life (Schore, 2001b). As previously discussed, the inverted "U" patterns of tolerated levels of both dopamine (DA) and noradrenaline (NE) are set up during play, restorative repair, and touch during infancy (Schore, 2001a); consequently, throughout all life stages, levels outside of these relatively fixed ranges can contribute to neurotoxicity, and subsequent synaptic pruning and cell death (Schore, 2001b). Furthermore, as schizophrenics are characterized as having both low baseline NE (Kokkinidis & Anisman, 1980), and high DA levels (Kapur et al., 1998; Remington, Kapur & Zipursky, 1998; Robbins, 1990), they are at higher risk for falling outside of these optimal ranges during times of even minor strain, resulting in the easy induction of over-

pruning that may contribute to the development of the disorder.

Interestingly, synaptic death via this imbalance may manifest as positive symptoms through the attention deficits, such as difficulty disregarding irrelevant stimuli, and heightened arousal that are found in schizophrenic patients, and which have been correlated in studies to low NE and high DA, respectively (Firestone & Marshall, 2003). These findings strongly imply that damage specific to the synapses of the right orbitofrontal cortex may result from the high DA/low NE profile, as it is this area that is said to play a special role in sustaining attention over time, and as such, evidence of attention deficits imply disruption to the function of this structure (Ruekert & Graftman, 1996).

This focused damage may be due to the fact that the homeostasis between DA and NE in this area is particularly delicate, with small changes in the DA/NE balance quickly leading to neurotoxicity (Shore, 2001b). Consequently, its synaptic connections may be most vulnerable to subtle changes in the environment, especially those that involve attachment and emotion, as these functions are dominant in the right orbitofrontal region (Schore, 2001 a & b). This mechanism may partially explain the impact of EE on

relapse history, as the negativity displayed by family members may directly contribute to the reductions in the complexity of this structure that are characteristic of the progression of the disease (Firestone & Marshall, 2003).

In addition, this already overactive stress response may be even further exacerbated by past conditioning characteristic of the insecure attachment patterns displayed by most schizophrenics (Schore, 2001b). Specifically, because of their negative histories, they are unlikely to seek out interpersonal interaction during stressful life experiences (Schore, 2001b). This lack of active coping skills results from the belief that the attachment relationship is not safe, causing a stress response during periods of intimacy (Schore, 2001b), and reducing the possibility for homeostasis to be recovered quickly through its most efficient means, as this requires the seeking out of others for comfort in order to reduce stress-related physiological reactions (Schore, 2001a). Therefore, the damage caused by stress may not only be enhanced through the high DA/low NE profile, but also prolonged in individuals who have experienced disrupted attachment, contributing to further damage to the cerebral cortex in the event of any stress-related experience, and consequently, to the chaotic

behavior characteristic of the disorder in affected bilateral individuals.

*Adult attachment relationships.*

As the effects of early attachment relationships seem of significance, it follows deductively that positive attachment experiences since the third year of life might act as buffers from some of these effects. For instance, if the susceptible individual were to establish a secure bond later in life, they may eventually overcome their early fear of intimacy and learn interactive coping strategies that might assist them in quickly regaining homeostasis following stress, thus ending the negative cycle. Just as the presence of the caregiver"s face in play generates high levels of positive affect in the infant (Schore, 2001a), so to do similar encounters later in life, and as such, individuals capable of reversing their attachment style, at least in certain relationships, may learn to overcome adversity, and broaden their DA/NE tolerance levels before triggering the stress response, and inducing damage.

Conversely, someone with a prior secure attachment style who has undergone trauma, and subsequently seen a reversal to an insecure form of attachment, would be at an

increased risk at this stage. Though not as vulnerable as their early-disrupted counterparts, this trend may partially explain the high positive correlations between trauma, PTSD, and the development of schizophrenia.

*The role of sex hormones.*

In addition to NE/DA, research has implicated sex hormones in synaptic pruning. Studies have shown increases in the number of synapses, cell growth, and proliferation of axons upon exposure to both high estrogen (Naftolin et al., 1990), and progesterone (Schore, 2001a), and enhanced metabolic activity and subsequent synaptic maintenance in the right hemisphere following exposure to elevated testosterone (Storfer, 2001). In fact, sex hormones are thought to also exhibit an inverted “U” range of optimal levels, as overly high or low amounts of testosterone were linked to reductions of IQ, especially in the visuospatial tasks of the right hemisphere of a male subject pool (Tan & Tan, 1998). In fact, IQs as high as 130 were only found in male individuals displaying the optimal range of testosterone levels (Tan & Tan, 1998), indicating that drops in or excesses of the hormone may negatively impact the development of giftedness. As such, it may be postulated

that sex hormones help to maintain synapses, especially in the right hemisphere, and therefore that a steep drop in their levels may be required for the development of schizophrenia. As these reductions occur following adolescence in males, and near the end of the optimal reproductive period in females, this may contribute to the discrepancy in age of onset between the sexes, and also to the lack of symptom presentation in affected individuals until adulthood.

*Conclusion*

However, with all of these factors interacting in the adult state, what is it that leads to the increased susceptibility of symmetrical individuals? Similar to the attachment hypothesis, the answer may be found in the increased surface area, and subsequently, the longer axons required for the proper organization of the bilateral brain. As such, trophic factors, such as improved relationships and optimal DA/NE and sex hormone levels, may have increased opportunity to enhance these individuals, resulting in giftedness, but also a larger opportunity to disrupt them if impaired. If this is, in fact, the case, it may go a long way towards explaining the links between symmetry and

psychosis by supporting the notion of increased vulnerability to both disaster and success in these individuals.

## CONCLUSION

Despite the sheer diversity of the causes and correlations related to this disorder, many of which have been excluded for parsimony‟s sake, none can be conclusively linked to every single presentation of schizophrenia (Berlim et al., 2003). With so many factors influencing synapse formation and retention, the convergent etiological hypothesis proposed in the first division of this paper gains credibility. What appears to be key in the acquisition of the disease is that particular synapses, namely those between hemispheres and those that inhibit the stress response, have significantly degenerated. Consequently, the notion of schizophrenia as a developmental disorder arising because of disruption in the pattern of interconnections crucial to the functioning of the symmetrical brain is also strengthened.

This may be true regardless of cause, however, and as such, whether loss of connectivity in any one particular individual results due to the presence of an inferior myelination gene, to obstetrics complications, to attachment

disruptions, or to later life stress may be less important than a realization of the particular vulnerability of the bilateral brain to both growth enhancing and inhibiting effects, whatever they may be. As such, the interconnectivity underlying thought processes might be more easily improved or damaged in symmetrical individuals, contributing to either exceptional giftedness or psychological disease.

In this vein, it is possible that a difference between the sexes may fall along similar lines. This conclusion is drawn from two findings; first, there are more men present in the symmetrical community as a whole, and consequently, more males in both the extremely gifted (Singh & O"Boyle, 2004), left handed (Geschwind & Galaburda, 1985), and schizophrenic populations (Berlim et al., 2003), indicating an increased presence of symmetry in male individuals. Secondly, however, in the general asymmetrical population, the average male, on the whole, shows increasing lateralization of function and reduced corpus callosum connectivity compared to female controls (De Lacoste-Utamsing & Holloway, 1982), which, together with the aforementioned, demonstrates a greater tendency in the male of our species towards the brain organization style of whatever orientation is dominant to his genotype. This

evidence supports the concept of a mixed-dominance symmetry gene being found on the X chromosome, as this would contribute to the greater incidence and severity of the disease in males due to a lack of a balancing gene present on the other X chromosome in females. Consequently, males may be more susceptible on the genetic level to both exclusive symmetry or asymmetry acquisition. However, they may also be more sensitive to environment, due the metabolic surges caused by their dominant sex hormone, testosterone, as this contributes to brain plasticity, and thus to a greater possibility for both growth and damage. As such, these two mechanisms may account for the larger proportions of men in both gifted and schizophrenic populations.

Regardless of sex, however, the potential of the symmetrical individual to both great accomplishments and great weaknesses carries strong implications for the prevention and treatment of psychosis. Firstly, at an incidence rate of 1%, schizophrenia remains a problem for the population at large, and should be handled as such. Therefore, public health initiatives focused on educating the public about the special needs, risks and benefits associated with parenting symmetrical babies, may prove a

good first step towards realizing these individuals‟ potentials, and possibly avoiding some of their pitfalls in the future.

Furthermore, and perhaps most importantly, I would like to propose that we consider including attachment therapy as part of the first line of treatment for patients presenting as being in the prodromal period of psychosis. The adverse affects that insecure attachment styles have on synaptic formation patterns stay with an individual throughout life, dictating their heightened stress response, and resulting in neurological damage that exacerbates the disease; thus subpar attachment styles must first be broken if we wish to assist a prodromal individual and prevent a psychotic episode. If we look back and recall that environment interjects into symptom presentation through its affects on synaptic use, we can begin to realize that this form of talk therapy may increase the likelihood that the patient will retain certain key synaptic connections through their use both in therapy, and via the eventual learning of strategies to quickly re-achieve homeostasis following stress, such as through interactive coping skills. In addition, the teaching of reciprocal facial signaling, communication skills, and appropriate affect expression may be integral to

assisting schizophrenic individuals in forming intimate connections with others, thus strengthening their support system and further buffering them from relapse. In fact, this form of therapy may prove beneficial to even securely attached bilateral individuals in order to strengthen these active coping responses and interpersonal skills that seem crucial in the prevention of symptom presentation.

Finally, I would like to restate the importance of my point that comparisons in later studies should not be made to the population as a whole, but only within the community of symmetrical individuals in any further attempts to conceptualize the disease. With such striking and diverse combinations of symptomatology, it is no wonder that so many factors play a role in schizophrenia"s development and progression. Therefore, my hope is only that through my attempts to parallel and differentiate the various presentations of bilaterality, that I may have raised some interesting questions worth disproving in future research concerning these individuals.

# REFERENCE LIST

Arnsten, A.F.T., Steere, J.C. & Hunt, R.D. (1996). The contribution of a2-noradrenergic mechanisms to prefrontal cortical cognitive function. Potential significance for attention-deficit hyperactivity disorder. *Archives of General Psychiatry, 53,* 448-455.

Badcock, J.C., Dragovic, M., Waters, F.A. & Jablensky, A. (2005). Dimensions of intelligence in schizophrenia: evidence from patients with preserved, deteriorated and compromised intellect. *Journal of Psychiatry Research, 39 (1),* 11-19.

Baxter, M.G., Parker, A., Lindner, C.C.C., Izquierdo, A.D. & Murray, E.A. (2000). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *Journal of Neuroscience, 20,* 4311-4319.

Beebe, B. Lachmann, F.M. (1994). Representations and internalization in infancy: Three principles of salience. *Psychoanalytic Psychology, 11,* 127-165.

Benbow, C.P. (1986). Physiological correlates of extreme intellectual precocity. *Neuropsychologica, 24,* 719-725.

Boog, G. (2004). Obstetrical complications of subsequent schizophrenia in adiclescent and young adult offsprings: Is there a relationship? *European Journal of Obstetrics and Gynecology and Reproductive Biology, 114,* 130-136.

Bowlby, J. (1969). *Attachment and loss, vol. 1: Attachment.* New York, NY: Basic Books.

Brown, G.W., Carstairs, G.M. & Topping, G. (1958). Post-hospital adjustment of chronic mental patients. *The Lancet, 2,* 685-689.

Brune, M. (2004). Schizophrenia – an evolutionary enigma? *Neuroscience and Biobehavioral Reviews, 28,* 41-53.

Cannon, T.D., Barr, C.E. & Mednick, S.A. (1991). Genetic and perinatal factors in the etiology of schizophrenia.

In E.F. Walker (Ed.), *Schizophrenia: A Life-Course Developmental Perspective.* San Diego, CA: Academic Press.

Chugani, H.T. (1996). Neuroimaging f developmental nonlinearity and developmental pathologies. In R.W. Thatcher, G. R. Lyon, J. Rumsey & N. Krasnegor (Eds.), *Developmental Neuroimaging: Mapping the Development of Brain and Behavior.* San Diego, CA: Academic Press.

Cole, J.D. & Kazarian, S.S. (1993). Predictive validity of the level of expressed emotion (LEE) scale: Readmission follow-up data for 1-, 2-, and 5-year periods. *Journal of Clinical Psychology, 49,* 216-218.

Coplan, J.D, Rtost, R.C., Owens, M.J., Cooper, T.B., Gorman, J.M., Nemeroff, C.B & Rosenblum, L.A. (1998). Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. *Archives of General Psychiatry, 55,* 473-477.

Crow, T.J. (1997). Is schizophrenia the price that Homo sapiens pays for language? *Schizophrenia Research, 28,* 127-141.

Crow, T.J. (1990). The continuum of psychosis and its genetic origins – the sixty-fifth maudsley lecture. *British Journal of Psychiatry, 156,* 788-797.

Crow, T.J., & Done, D.J. (1986). Age of onset of schizophrenia in siblings: a test of the contagion hypothesis. *Journal of Psychiatric Research, 18,* 107-117.

De Lacoste-Utamsing, C. & Holloway, R.L. (1982). Sexual dimorphism in the human corpus callosum. *Science, 216 (4553),* 1431-1432.

Driesen, N.R., & Raz, N. (1995). The influence of sex, age, and handedness on corpus callosum morphology: A meta-analysis. *Psychobiology, 23,* 240-247.

Ehrlich, P. & Chiaramonte, L. (2003). *What your doctor may not tell you about children's allergies and asthma.* Lebanon, IN: Warner Books.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in synaptic elimination during adolescence? *Journal of Psychiatric Research, 17,* 319-334.

Feldman, R., Greenbaum, C.W. & Yirmiya, N. (1999). Mother-infant affect synchrony as an antecedent of the emergence of self-control. *Developmental Psychology, 35,* 223-231.

Filloux, F. & Townsend, J.J. (1993). Pre- and postsynaptic neurotoxic effects of dopamine demonstrated by intrastriatal injection. *Experimental Neurology, 119,* 79-88.

Firestone, P. & Marshall, W.L. (2003). *Abnormal Psychology; 2nd Edition.* Toronto, ON: Pearson Education Canada Inc.

Flashman, L.A., Saykin, A.J., Roth, R.M., Ricketts, S.M., Vidaver, R.M. & McAllister, T.W. et al. (2003). Brain activation patterns associated with listening to trauma-related words in patients with schizophrenia and healthy controls: A preliminary fMRI study. *Schizophrenia Research, 60 (1),* 217.

Fogel, A. & Branco, A.U. (1997). Metacommunication as a source of indeterminism in relationship development. In A. Fogel, M.C.D.P. Lyra, & J. Valsinger (Eds.), *Dynamics and Indeterminism in Developmental and Social Processes.* Mahweh, NJ: Erlbaum.

Geschwind, N., & Galaburda, A.M. (1985). Cerebral lateralization: Biological mechanisms, associations, and pathology; I: A hypothesis and a program for research. *Archives of Nuerology, 42,* 428-459.

Gibbons, A. (1998). Solving the brain"s energy crisis. *Science, 280,* 1345-1347.

Hogarty, G.E., Anderson, C.M., Reiss, D.J., Kornblith, S.J., Greenwald, D.P., Javna, C.D. & Madonia, M.J. (1986).

Family psychoeducation, social skills training, and maintnance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. *Archives of General Psychiatry, 43,* 633-642.

Hollingshead, A.B. & Redlich, F.C. (1958). *Social class and mental illness: A community study.* New York, NY: Wiley.

Isaacs, E.B., Edmonds, C.J., Chong, W.K., Lucas, A., Morley, R. & Gadian, D.G. (2004). Brain morphometry and IQ measurements in preterm children. *Brain, 127,* 2595-2607.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Kotten, A., Cooper, J.E., et al. (1992). Schizophrenia: Manifestations, incidence and course in different cultures. A World Health Organization ten country study. *Psychological Medicine, 20,* 1-97.

Jackson, C., Knott, C., Skeate, A. & Birchwood, M. (2004). The trauma of first episode psychosis: The role of

cognitive mediation. *Australian and New Zealand Journal of Psychiatry, 38 (5),* 327-333.

Kalin, N.H., Shelton, S.E. & Lynn, D.E. (1995). Opiate systems in mother and infant primates coordinate intimate contact during reunion. *Psychoeuroendocrinology, 20,* 735-742.

Kapur, S., Zipursky, R.B., Remington, G., Jones, C., DaSilva, J., Wilson, A.A. & Houle, S. (1998). R-HT2 receptor occupancy of olanzapine in schizophrnia: A PET investigation. *American Journal of Psychiatry, 155,* 921-928.

Kazarian, S.S. (1992). The measurement of expressed emotion: A review. *Canadian Journal of Psychiatry, 37,* 51-56.

Keshavan, M.S., Anderson, S., & Pettegrew, J.W. (1994). Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothsis revisited. *Journal of Psychiatric Research, 28 (3),* 239-265.

Kokkinidis, L. & Anisman, H. (1980). Amphetamine models of paranoid schizophrenia: An overview and elaboration of animal experimentation. *Psychological Bulletin, 88,* 551-579.

Kwon, J.S., McCarley, R.W., & Hirayasu, Y. Left planum temporale volume reduction in schizophrenia. *Archives of General Psychiatry, 56,* 142-148.

Lambert, S.R. (2002). Are there more exotropes than esotropes in Hong Kong? *British Journal of Ophthalmology, 86,* 835-836.

Leader, L.R., Baillie, P. & Martin, B. (1982). The assessment and significance of habituation to a repeated stimulus by the human fetus. *Early Human Development*, *7,* 211-219.

Lecanuet, J.P. Granier-Deferre, C. & Busnel, M.C. (1988). Fetal cardiac and motor responses to octave-band noises as a function of cerebral frequency, intensity and heart rate variability. *Early Human Development*, *18,* 81-93.

Lemke, H. & Lange, H. (2002). Childhood infections and autoimmune diseases. *New England Journal of Medicine, 346 (22),* 1749-1750.

Levin, B.E. & Routh, V.H. (1996). Role of the brain in energy balance and obesity. *American Journal of Physiology, 40,* R491-R500.

Main, M. & Solomon, J. (1986). Discovery of an insecure-disorganized/disoriented attachment pattern: Procedures, findings and implications for the classification of behavior. In T.B. Brazelton & M.W. Yogman (Eds.), *Affective Development in Infancy.* Norwood, NJ: Ablex.

Martin, L.J., Spicer, D.M., Lewis, M.H., Gluck, J.P. & Cork, L.C. (1991). Social deprivation of infant rhesus monkeys alters the chemoarchitecture of the brain: 1. Subcortical regions. *Journal of Neuroscience, 11,* 3344-3358.

May, P.B., DeMarco, K., London, E.B., Thompson, R., Mento, T.L., Buscemi, L. & Cody, R. (2001). Ventricular enlargement in adults with profound mental retardation who demonstrate violent/destructive behaviors. *The Journal of Neuropsychiatry and Clinical Neurosciences, 13,* 96-100.

McDonald, B., Highley, J.R., Walker, M.A., Herron, B.M., Cooper, S.J., Esiri, M.M. et al. (2000). Anomalous asymmetry of fusiform and parahippocampal gyrus gray mater in schizophrenia: a postmortem study. *American Journal of Psychiatry, 157,* 40-47.

McManus, C. (2002). *Right hand, left hand: the origins of asymmetry in brains, bodies, atoms, and cultures.* London: Windenfield & Nicholson.

Mino, Y., Oshima, I., Tsyda, T., & Okagami, K. (2000). No relationship between schizophrenic birth and influenza epidemics in Japan. *Journal of Psychiatric Research, 34,* 133-138.

Mueser, K.T., Rosenberg, S.D., Goodman, L.A. & Trumbetta, S.L. (2002). Trauma, PTSD, and the course of severe mental illness: An interactive model. *Schizophrenia Research, 53 (1-2),* 123-143.

Naftolin, F., Garcia-Segura, L.M. & Keefe, D. (1990). Estrogen effects on the synaptology and neural membranes of the rat hypothalamic arcuate nucleus. *Biological Reproductions, 42,* 21-28.

Norman, R.M.G. & Malla, A.K. (1993). Stressful life events and schizophrenia. I. A review of the literature. *British Journal of Psychiatry, 162,* 166-174.

Nottebohm, F. (1976). Neural lateralization of vocal control in a passerine bird. *Journal of Experimental Zoology, 177,* 229–262.

O"Boyle, M.W., Alexander, J.E. & Benbow, C.P. (1991). A new millennium in cognitive neuropsychology research: The era of individual differences. *Brain and Cognition, 42,* 135-138.

O"Boyle, M.W., Benbow, C.P. & Alexander, J.E. (1995). Sex differences, hemispheric laterality, and associated brain activity in the intellectually gifted. *Developmental Neuropsychology, 11,* 415-443.

Petty, R.G. (1999). Structural asymmetries of the human brain and their disturbance in schizophrnia. *Schizophrenia Bulletin, 25,* 121-139.

Remington, G., Kapur, S. & Zipursky, R. (1998). The relationship between risperidone plasma levels and dopamine D2 occupancy: A positron emission tomography study. *Journal of Clinical Psychopharmacology, 18,* 82-83.

Resnick, S.G., Bond, G.R. & Mueser, K.T. (2003). Trauma and posttraumatic stress disorder in people with schizophrenia. *Journal of Abnormal Psychology, 112 (3),* 415-423.

Robbins, T.W. (1990). The case for frontostriatal dysfunction in schizophrenia. *Schizophrenia Bulletin, 16,* 391-402.

Robbins, T.W. & Everitt, B.J. (1996). Neurobehavioral mechanisms of reward and motivation. *Current Opinions in Neurobiology, 6,* 228-236.

Rosen, G.D. (1996). Cellular, morphometric, ontogenetic and connectional substrates of anatomic asymmetry. *Neuroscience & Biobehavioral Reviews, 20,* 607-615.

Ruekert, L. & Graftman, J. (1996). Sustained attention deficits in patients with right frontal lesions, *Neuropsychologica, 10,* 953-963.

Ryan, R.M., Kuhl, J. & Deci, E.L. (1997). Nature and autonomy: An organizational view of social and neurobiological aspects of self-regulation in behavior and development. *Development and Psychopathology, 9,* 701-728.

Schore, A.N. (1994). *Affect Regulation and the Origin of the Self: The Neurobiology of Emotional Development.* Mahwah, NJ: Erlbaum.

Schore, A.N. (2001a). Effects of a secure attachment relationship on right brain development, affect regulation, and infant mental health. *Infant Mental Health Journal, 22 (1-2),* 7-66.

Schore, A.N. (2001b). The effects of early relational trauma on right brain development, affect regulation, and infant mental health. *Infant Mental Health Journal, 22 (1-2),* 201-269.

Sham, P.C., O"Callaghan, E., Takei, N., Murray, G.K., Hare, E.H, & Murray, R.M. (1992). Schizophrenia following prenatal exposure to influenza epidemics between 1939 and 1960. *British Journal of Psychiatry, 160,* 461-466.

Sherman, G.F., Garbanati, J.A., Rosen, G.D., Yutzey, D.A. & Denenberg, V.H. (1980). Brain and behavioral asymmetries for spatial preference in rats. *Brain Research, 192,* 61–67.

Shors, T.J. & Miesegaes, G. (2002). Testosterone in utero and at birth dictates how stressful experience will

affect learning in adulthood. *Proceedings of the National Academy of Sciences of America, 99 (21),* 13955-13960.

Singh, H. & O‟Boyle, M.W. (2004). Interhemispheric interaction during global-local processing in mathematically gifted adolescents, average-ability youth, and college students. *Neuropsychology, 18 (2),* 371-377.

Storfer, M.D. (2001). The parallel increase in brain size, intelligence and myopia. *Psycholoquy, 12 (13).*

Tan, U. & Tan, M. (1998). The curvelinear correlations between the total testosterone levels and fluid intelligence in men and women. *International Journal of Neuroscience, 94,* 55-61.

Thimble, M.H. (1990). Psychopathology of frontal lobe syndromes. *Seminars in Neurology, 10 (3).*

Tronick, E.Z. (1989). Emotions and emotional communication in infants. *American Psychologist, 44,* 112-119.

Tucker, D.M. (1992). Developing emotions and cortical networks. In M.R. Gunnar & C.A. Nelson (Eds.), *Minnesota Symposium on Child Psychology; Vol. 24: Developmental Behavioral Neuroscience.* Hillsdale, NJ: Erlbaum.

Vasta, R., Haith, M.M. & Miller, S.A. (1999). *Child Psychology: the Modern Science; 3rd Edition.* New York, NY: Wiley & Sons, Inc.

World Health Organization. (1973). *Report of the International Pilot Study of Schizophrenia, Volume I.* Geneva: World Health Organization.

Yamada, H., Sadato, N., Konishi, Y., Kimura, K., Tanaka, M., Yonekura, Y. & Ishii, Y. (1997). A rapid brain metabolic change in infants detected by fMRI. *NeuroReport, 8,* 3775-3778.

Yamada, H., Sadato, N., Konishi, Y., Muramoto, S., Kimura, K., & Tanaka, M., et al. (2000). A milestone for normal development of the infantile brain detected by functional MRI. *Neurology, 55,* 218-223.

# APPENDIX

*The Proposed Relationship Between Cortical Symmetry, Myelination, and Incidence of Schizophrenia*