Negative Symptoms, Chapter 6

SAMPLE CHAPTER FROM THE PEER-REVIEWED BOOK

MENTAL ILLNESS DEFINED
CONTINUUM, REGULATION, AND DEFENSE

BRAD BOWINS, MD, F.R.C.P.(C)

https://bradbowinsbooks.com/mental-illness-defined/

https://www.routledge.com/Mental-Illness-Defined-Continuums-Regulation-and-Defense/Bowins/p/book/9781138200609

The division of symptoms associated with schizophrenia into positive and negative does appear to have merit. Positive symptoms involve distortions and typically added mental activity beyond what is normal, whereas negative symptoms entail something removed from what is normal, and usually reduced mental activity (Arango et al, 2004; Bowins, 2011; Langdon et al, 2014). In addition, differences in course of illness, symptoms, response to treatment, neurochemistry relevant to pharmacological intervention, neurobiology, neuropsychological functioning, family history, premorbid adjustment, and risk factors, support such a distinction (Arango et al, 2004; Carpenter et al, 1999; Fanous et al, 2001; Fenton & McGlashan, 1994; Horan & Blanchard, 2003; Kirpatrick et al, 2000; Kirkpatrick et al, 2001; Klemm et al, 2006; Lahti et al, 2001; Malaspina & Coleman, 2003; Pogue-Geile & Harrow, 1984; Vaiva et al, 2002). Psychosis (positive symptoms) tends to be episodic and responds very well to antipsychotic medications that work by blocking dopamine, while negative symptoms develop gradually in a long prodromal phase and are quite resilient to treatment, with extensive efforts such as cognitive remediation often producing limited gains that frequently do not generalize beyond the task (Addington & Addington, 2009; Amador et al, 1999; Arango et al, 2004; Buchanan et al, 1990; Dickinson et al, 2010; Galletly, 2009; McCullumsmith, 2004). Negative symptoms do not respond well at all do dopamine blockage, and if anything seem to involve alternative neurochemical receptors and transmitters, such as serotonin receptors (including 5HT-1A and 5HT-2A), glycine, and glutamate (NMDA receptor subtype) (Galletly, 2009; Goff & Coyle, 2001; Gupta & Kulhara, 2010; Heresco-Levy, 1999; Javitt, 2008; Lane et al, 2005; Uchida et al, 2011). Also of fundamental importance cognitive impairments are much more strongly linked to negative than positive symptoms (Bilder et al, 2000; Daly et al, 2012; Helldin et al, 2006; Kimhy et al, 2005; Lucas et al, 2004; Rossi et al, 1997; Smith et al, 2009).

Another key issue is that if positive and negative symptoms are of the same type, they would be more tightly correlated in symptom presentations, with more

extensive positive symptoms related to more intense negative symptoms. However, what transpires is a range of both, with so-called negative symptom (deficit) schizophrenia at one end of a continuum characterized by mainly negative symptoms and fewer positive symptoms, and positive symptom (non-deficit) schizophrenia involving predominately psychosis and fewer negative symptoms (Amador et al, 1999; Arango et al, 2004; Bowins, 2011; Galderisi et al, 2008; Kimhy et al, 2006; Kirkpatrick & Buchanan, 1990; Kirkpatrick et al, 2000; Peralta & Cuesta, 2004). Countering the possibility that positive and negative symptoms themselves occur along the same continuum, with negative and positive symptom extremes at opposite poles, this arrangement would mean that the symptom types trade off, more positive meaning less negative and vice-versa, whereas a mixture of prominent negative and positive symptoms often transpires. Hence, there must be two separate continuums.

Part of the confusion regarding whether or not positive and negative symptoms are distinct, is a failure to appreciate the range of negative symptoms and what they actually mean. In some instances researchers focus on a select symptom or type that might be linked to psychosis if taken in isolation. For example, over the last several years there has been somewhat of an emphasis on motivation as the primary negative symptom, at least by those conducting research on newer antipsychotics. This occurrence is quite likely due to how of all the negative symptoms, motivation might be one that could respond to antipsychotics, given how motivational issues arise from so many different sources including depression. An important distinction here is between primary and secondary negative symptoms, with the former arising from a disease process inherent to the illness, and secondary symptoms from other sources such as depression or side effects of certain medications (Kaiser et al, 2011). While it appears as if there is improvement in the primary negative symptom, what is often occurring is resolution of the secondary negative symptoms, such as a second-generation antipsychotic increasing motivation by resolving depression, or removal of the amotivation side effect of first-generation antipsychotics. Negative symptoms can be cherry picked to support certain agendas, with those having strong secondary causation often the focus, due to how they are more likely to respond to interventions.

What negative symptoms actually mean and refer to though is much more extensive, essentially being a lack of the cognitive abilities that make us human, or what might be referred to as human specific cognition (Bowins, 2011; Burns, 2009; Fiszdon et al, 2007). The term human specific cognition is not meant to imply characteristics entirely absent in other species or our ancestors during evolution, as traits are derived from preexisting templates due to how natural selection conserves resources by building on what has come before (Darwin, 1858/1958). It instead refers to the compilation of cognitive abilities that distinguish us behaviorally from other species. To avoid the potential charge that negative symptoms are being cherry picked to satisfy an agenda, it is best to be expansive regarding what constitutes human specific cognition, and when absent or diminished, produce negative symptoms.

In line with a comprehensive coverage of human specific cognition, negative symptoms include deficits in basic cognition, social cognition, and motivational

states (often referred to as absence symptoms). A stable and enduring subset of these negative symptoms referred to as the deficit state has been identified, including restricted affect, diminished emotional range, poverty of speech, reduced interests, diminished sense of purpose, and diminished social drive (Amador et al, 1999; Carpenter, 1988; Kirkpatrick et al 1989; Kulhara & Chandiramani, 1990). In keeping with the notion of expanding the range to be fully inclusive, the focus will not be on this subset. Basic cognitive symptoms consist of deficits in executive functioning, with executive functions referring to the following (Ashby et al, 1999; Bilder et al, 2000; Elvevag & Goldberg, 2000; Fiszdon et al, 2007; Gross & Grossman, 2010; Keefe & Fenton, 2007; Morice & Delahunty, 1996; Reichenberg et al, 2010):

Working memory—The ability to hold information in short term memory allowing time to process it as required for the given mental activity.

Initiation—The capacity to begin a task or activity, or independently generate ideas.
Inhibition—The ability to stop behavior including thoughts, actions, and impulses.

Cognitive Flexibility (set shifting)—Being able to flexibly shift from one thought or behavior to another, in line with the demands of the situation.

Task Completion—The ability to carry through with a task to its endpoint without distraction.

Attention—Being able to focus on a mental or physical task sufficiently long enough to complete it.

Planning—The capacity to anticipate future events and prepare accordingly.

Organization—The ability to arrange thoughts, items, and behavior in an orderly and logical fashion or sequence.

Monitoring—The ability to assess performance during and after a task to ensure completion.

Multitasking—The capacity to perform different functions during the same short time frame.

Some of the executive functions depend on others, such as cognitive flexibility or set shifting relying on the ability to inhibit prior actions and responses (Gross & Grossman, 2010). Multitasking is a higher-level executive function requiring several others such as inhibition, set shifting, attention, monitoring, organizing, and task completion (Gross & Grossman, 2010). Basic cognition can also be expanded to more extensive abilities including problem solving, the ability to generalize beyond past experience, and overall or fluid intelligence, so it is not fully synonymous with executive functions, although in most instances it refers to the latter (Fiszdon et al, 2007; Ivleva et al, 2012b). Capacities like problem solving, the ability to generalize,

and overall intelligence actually do rely on executive functions (Bilder et al, 2000; Elvevag & Goldberg, 2000; Fiszdon et al, 2007; Gross & Grossman, 2010; Ivleva et al, 2012 b; Keefe & Fenton, 2007; Morice & Delahunty, 1996; Reichenberg et al, 2010). Working memory in particular appears to be crucial for a diverse range of cognitive abilities (Johnson et al, 2013).

Basic cognition is understandably reliant on intact neural functioning (Collette et al, 2005; Eisenberg & Berman, 2010; Gross & Grossman, 2010; Monchi et al, 2006; Smith & Jonides, 1997). Many of the underlying neural structures overlap but there is independence, as is evident during conditions such as frontotemporal degeneration, where difficulties with organizing material stands out (Gross & Grossman, 2010). Indeed, several disease processes involving distinct brain regions can produce impairments to certain executive functions independent of others (Godefroy, 1999; Gross & Grossman, 2010). Furthermore, correlations in performance across executive functions are quite low (Gross & Grossman, 2010; Miyake et al, 2000).

The topic of what brain regions are linked to specific executive functions is an extensive one, beyond the realm of what can reasonably be covered in this chapter. However, some all encompassing points will be made regarding this topic. Generally speaking, executive functions rely on both structures, and also specific and intact connections (connectivity) between different brain regions (Eisenberg & Berman, 2010; Gross & Grossman, 2010). Regarding structures the frontal lobes, and particularly the prefrontal cortex (PFC), are highly implicated (Gross & Grossman, 2010). Equally important, though, is connectivity between various cortical structures (cortical-cortical), and cortical and subcortical (cortical-subcortical) (Gross & Grossman, 2010). Functional neuroimaging studies for example have suggested that frontoparietal connections are critical to several executive functions, including working memory, set shifting (cognitive flexibility), and inhibition (Collette et al, 2005; Gross & Grossman, 2010; Smith & Jonides, 1997). Connections between cortical regions and the basal ganglia (subcortical) appear to be important for planning (Gross & Grossman, 2010; Monchi et al, 2006). Integrity of both gray and white matter is also crucial for executive functions, with white matter the platform for connectivity (Eisenberg & Berman, 2010). The linkages between gray matter and white matter (connectivity), instrumental for executive functions, can be viewed as neural networks or neural circuits, with particular patterns of structures and connections associated with each executive function (Eisenberg & Berman, 2010; Gross & Grossman, 2010). Damage or impairment to the neural networks associated with executive functions, does impact negatively on executive functions, and in turn adaptive behavior (Eisenberg & Berman, 2010; Gross & Grossman, 2010; Mateer, 1999). This is a key reason why impaired neurocognition is tightly linked to negative symptoms (Bilder et al, 2000; Daly et al, 2012; Helldin et al, 2006; Kimhy et al, 2005; Lucas et al, 2004; Rossi et al, 1997).

Social cognitive symptoms, the second type of negative symptoms, include impairments in how people think about themselves, others, social situations and interactions (so-called Theory of Mind deficits), plus emotional information processing, understanding complex social-emotional scenarios such as irony and

sarcasm, and social drive limitations (Bediou et al, 2007; Combs et al, 2013; De Jong et al, 2013; Fett et al, 2011; Fiszdon et al, 2007; Kirkpatrick & Buchanan, 1990; Rapp et al, 2014). Emotional information processing is crucial for social cognition, and a key component of emotional information processing is facial expression recognition, with deficits greatly impairing social cognition (Bediou et al, 2007). Connectivity between the amygdala and both the PFC and temporal cortex are necessary for facial expression recognition (Bediou et al, 2007), demonstrating how as with basic cognition both structures and connectivity between regions is crucial. Lesions to the neural circuits providing the capacity for social affiliation and other social behaviors, results in diminished social drive, poverty of speech, and blunted affect, all involved in the deficit syndrome (Kirkpatrick & Buchanan, 1990).

Social complexity is linked to larger brain size in animals, and social isolation not only impairs social cognition but also basic cognition (Cacioppo & Cacioppo, 2012). Not surprisingly, social cognition impacts heavily on social outcomes in schizophrenia, accounting for 23% of the variance, based on the work of Fett et al (2011) who analyzed outcomes from 52 research projects. Neurocognitive deficits linked to basic cognition accounted for 15% of the variance in social outcomes (Fett et al, 2011). Social cognition links to emotional intelligence that predicts success not only socially, but occupationally, more than does general intelligence (Goleman, 1995). We are a social species and those lacking solid social cognition often fair quite poorly.

The third type of negative symptom, motivational or absence states, consist of apathy, avolition, anhedonia, alogia, motor retardation, affective flattening, poverty of speech, and absence of play and curiosity (Ballmaier et al, 2008; Bemporad, 1991; Mahurin et al, 1998;). The importance of these motivational states to healthy functioning is found in how they are well represented in the deficit syndrome, with restricted affect, poverty of speech, reduced interests, and diminished sense of purpose (Amador et al, 1999; Carpenter et al, 1988; Kirkpatrick et al, 1989; Kulhara & Chandiramani, 1990). Amotivational symptoms appear to be present is the normal population as well as the clinical population, with much higher levels in those with schizophrenia (Ballmaier et al, 2008; Kaiser et al, 2011).

Human Specific Cognition to Negative Symptoms

As we have seen, basic cognition, social cognition, and motivational states comprise human specific cognition (Bowins, 2011; Burns, 2009; Fiszdon et al, 2007). Negative symptoms involve an absence or reduction in these cognitive abilities, but why does this type of impairment occur? Why is always a difficult question and there are undoubtedly a multitude of reasons general and specific, but a few general ones do stand out, such as entropy (Bowins, 2011). Entropy provides a measure of the disorder in a system, higher entropy equating with greater disorder, and low entropy lesser (Atkins, 2007; Deutsch, 1998). In the absence of any other activity in the universe, matter will progress from order to disorder due to entropy (Atkins, 2007; Deutsch, 1998). Highly ordered structures are very vulnerable to this natural shift from order to disorder, and one of the most highly ordered structures in the universe is probably human specific cognition, and equivalent cognition in other

intelligent life forms (Bowins, 2011). Hence, the second law of thermodynamics (entropy) is acting in an ongoing fashion to breakdown the orderly structuring of human specific cognition.

Entropy is assisted in its erosion of human specific cognition by the nature of these capacities, in particular, their relatively recent evolutionary origin (Bowins, 2011). Human cognition arose approximately 200,000 years ago, and although relative to our own lifespan this seems long, it is a mere drop in the evolutionary bucket (Glantz, & Pearce, 1989). Consequently, human specific cognition is less stable than processes that have been evolving over a much longer period, such as olfaction (Bowins, 2011). Entropy and the relative instability of human specific cognition interact, in that entropy is likely to have a greater impact on these less fixed and resilient highly ordered structures (Bowins, 2011). Worsening the situation is how human specific cognitive abilities mature over childhood and adolescence, leaving them highly vulnerable to the impact of entropy over a longer time period.

An additional general process that might help account for negative symptoms is a phenomenon derived from computer engineering known as the NP Complete Problem (Pavlus, 2012). Essentially, it refers to the process of getting to the endpoint, and how the finished state does not clearly detail the steps involved (Pavlus, 2012). For example, looking at a car does not tell you what steps were required to assemble it. Instead, an algorithm must suffice, but due to entropy and other issues there is about a 3% error rate from start to endpoint, or in other words the algorithm can only be about 97% accurate (Pavlus, 2012). Applied to neural systems there is likely a 3% error rate in their development (Pavlus, 2012). Now if that 3% impacts on the maturation of human specific cognition, highly likely due to how prominent the development of these capacities are, and their very ordered nature leaving them more vulnerable to the entropy, then human specific cognition will suffer producing negative symptoms. Due even to random variation some people will end up with significantly greater than the 3% error rate to human specific cognition.

In terms of more specific adverse influences on human specific cognition, and hence the development of negative symptoms, there are countless possibilities both genetic and environmental, and also how environmental inputs can activate or deactivate genes (epigenetic). Undoubtedly, there are multiple genes involved in the development of human specific cognitive abilities, and problems with any of these genes in isolation or combination, could result in negative symptoms, at least in the context of the more general influences mentioned. From an environmental perspective, numerous factors could play a role such as obstetrical complications impacting on the early development of human specific cognitive abilities, or infections. Some of these factors could result in the unhealthy expression of genes linked to human specific cognition, and via this epigenetic process produce negative symptoms. Indeed, the multitude of genetic, environmental, and epigenetic factors might make each person unique in the constellation of inputs, which in combination with the general influences mentioned above can result in impairments to human specific cognition and negative symptoms.

Given the diverse range of basic cognition, social cognition, and motivational states, deficits in these human specific cognitions would be expected to manifest in several different illnesses. However, negative symptoms are typically only associated with schizophrenia. In reality, several mental illnesses appear to be characterized by human specific cognitive deficits (Owen, 2012; Waltereit et al, 2014). Intellectual disability (formerly known as developmental delay and mental retardation) involves global deficits in basic cognition, and specific forms of learning impairments, such as for math or language, result from focal deficits in basic cognition related to the nature of the impairment (Owen, 2012; Waltereit et al, 2014). Autism spectrum disorders arise from global deficits in social cognition (Owen, 2012; Waltereit et al, 2014). Considering the extensive nature of the impairments to social cognition in this condition, and how critical this form of human specific cognition is to success, it is not surprising that barely 55% have any employment, including volunteer and part-time work, 6 years after leaving high school, with the rate of employment higher for those with Intellectual Disability (Volkmar & Wolf, 2013). Attention deficit hyperactivity disorder (ADHD) is another condition highly linked to negative symptoms, that appears to involve select deficits in basic cognition, such as attention, inhibition, set shifting, and also possibly some social cognition limitations related to emotional information processing (Oades, 1998; Owen, 2012; Purper-Ouakil & Franc, 2011)

Schizophrenia, the condition most associated with negative symptoms, entails deficits in basic cognition, social cognition, and motivational states, underscoring the severity of it and the extent to which it typically compromises adaptive functioning (Owen, 2012; Waltereit et al, 2014). Although bipolar disorder is not usually thought of in terms of negative symptoms, they are actually very prominent (Ancin et al, 2013; Blanchard et al, 1994; Brandt et al, 2014; Kuswanto et al, 2013; Nieto & Castellanous, 2011; Simonsen et al, 2008). The focus is on BPI consisting of depression and mania, because there is no clear association between hypomania, consistent with its 1-3 day expression, and negative symptoms independent of depression. Hypomania typically occurs in conjunction with depression probably as a defensive compensation (see the "Hypomania-Mania" chapter). Depression often entails secondary negative symptoms, such as amotivation and impairments in basic cognition, and also primary negative symptoms potentially confounding whether negative symptoms are linked to depression, hypomania, or both.

Research comparing negative symptoms in schizophrenia and bipolar disorder is important to consider. Overall the results indicate substantial negative symptoms in both conditions when BPI is focused on (Ancin et al, 2013; Blanchard et al, 1994; Brandt et al, 2014; Kuswanto et al, 2013; Nieto & Castellanous, 2011; Simonsen et al, 2008). Ancin et al (2013) compared 148 bipolar patients, 262 stable schizophrenics, and 108 healthy controls on a battery of neuropsychology tests. BPI and schizophrenia subjects both showed equal and widespread deficits in executive functioning, but BPII subjects (based on the 4-day criterion) only showed select impairments on planning and inhibitory tasks. Kuswanto et al (2013) and Ivleva et al (2012a) found similar levels of impairments to basic cognition in schizophrenic and bipolar subjects, but did not examine hypomania. The hypomania result from

the Ancin et al (2013) study demonstrates how negative features are very limited in this condition, given that impairments were only related to 2 executive functions, even when the standard diagnostic criteria for BPII are applied (Ancin et al, 2013). The results of a study by Simonsen et al (2008) comparing neurocognitive profiles between BPI and BPII also found fewer impairments with BPII using the minimum 4-day criteria. Furthermore, some of the deficits with BPII are likely linked to depression (Harvey, 2011).

Examining early onset schizophrenia and pediatric bipolar disorder, Nieto & Castellanous (2011) found similar impairments in cognitive performance (verbal learning and memory, information processing speed, and executive control) in the two groups, but those in the pediatric bipolar group were milder. Comparing adults with schizophrenia, bipolar disorder, and neither condition on a working memory task, Brandt et al (2014) found functional magnetic resonance imaging (fMRI) evidence for greater deficits in the schizophrenia group than bipolar group, who showed more damage than the normal group. Executive functions generally seem to be impaired in bipolar disorder even when not experiencing a manic episode (Arts et al, 2008). Focusing on anhedonia, Blanchard et al (1994) found less capacity for pleasure in schizophrenia than bipolar disorder. Anhedonia appears to be increased even in euthymic bipolar individuals, as well as remitted depressive patients, compared to healthy controls (Di Nicola et al, 2013). Atre-Vaidya et al (1998) discovered that anhedonia was related to memory impairments in those with bipolar disorder.

Negative symptoms are clearly associated with illnesses other than schizophrenia in a primary form, and not just secondary to the illness. They are a marker of severity as with their presence in BPI, but minimally in BPII. Even in depression, the presence of primary negative symptoms indicates a more severe illness, as expressed by psychosis (Coryell, 1997). At a proximal level, negative symptoms appear to arise from so-called dysconnectivity between various brain regions, both local and distal, because human specific cognition relies on the right connections between different cortical regions, and also between cortical and subcortical structures (Gross & Grossman, 2010). This reliance is evident from the role of connectivity in executive functioning examined earlier in the chapter. Dysconnectivity between brain regions involving deficient or excessive connectedness is a common finding in mental illnesses involving negative symptoms (Adler et al, 2004; Anticevic et al, 2013; Argyelan et al, 2014; Baker et al, 2014; Bartfield et al, 2014; Collin et al, 2013; Guo et al, 2014; Hong et al, 2015; Knochel et al, 2014; Kumar et al, 2014; Mamah et al, 2013; Meda et al, 2012; Pettersson-Yeo et al, 2011; Sharma et al, 2013; Siebenhuhner et al, 2013; Skudlarski et al, 2013; Stekelenburg et al, 2013; Uhlhaas; 2013). The literature pertaining to just schizophrenia and bipolar disorder is enormous and growing rapidly each year, and hence only limited studies will be reviewed to provide examples of how pivotal dysconnectivity is.

There are several instances of dysconnectivity common to both schizophrenia and BPI. White matter tracts so crucial for linking brain regions demonstrate substantial dysconnectivity in both conditions (Kumar et al, 2014; Skudlarski et al, 2013). The PFC, important for human specific cognition and also

regulation, shows a loss of white matter coherence (Adler et al, 2004). Frontoparietal control networks demonstrate reduced connectivity (Baker et al, 2014). Fronto/occipital connectivity to anterior default mode/PFC seems to be impaired in both conditions, but the same study also found differences such as meso/paralimbic to sensory-motor connectivity only altered in schizophrenia, and meso-paralimbic to fronto-temporal/paralimbic altered only in bipolar disorder (Meda et al, 2012). Mamah et al (2013) found decreased connectivity in both illnesses for cingulo-opercular to cerebellar neural networks, with a somewhat greater reduction in the schizophrenic group. Decreased cerebellar to salience network connectivity distinguished bipolar disorder patients, whereas decreased cingulo-opercular to salience network, cingulo-opercular to frontoparietal, and frontoparietal to cerebellar characterized schizophrenic subjects (Mamah et al, 2013). Inconsistent finding are common, such as with Baker et al (2014) mentioned above finding reduced connectivity with frontoparietal networks for both conditions, the same pattern not found by Mamah et al (2013). Dysconnectivity frequently appears to be more intense in schizophrenia than bipolar disorder. For example, Argyelan et al (2014) comparing global connectivity in schizophrenics, bipolar disorder patients, and normal individuals, found least in the latter group, and greatest global dysconnectivity in the schizophrenic group. Likewise, reductions in functional connectivity within the hippocampal network seem to be present in both schizophrenia and bipolar disorder, but more extensively in the former (Knochel et al, 2014).

Most of the results reported involve reduced connectivity between or within regions, but increased connectivity also occurs, such as increased amygdala-medial PFC connectivity in bipolar disorder (Anticevic et al, 2013). Long-range connectivity in schizophrenia appears to be increased, a problem attributed to failure to prune unneeded connections during the neurodevelopmental phase of adolescence (Guo et al, 2014). However, Sharma et al (2013) found reduced fronto-posterior connectivity. Compared to healthy subjects, in schizophrenia gray matter connectivity is both increased (such as left temporal and bilateral subcortical) and decreased (as with left frontal and bilateral subcortical) (Collin et al, 2013). The full extent and complexity of dysconnectivity patterns in schizophrenia is beyond the scope of this chapter, but interested readers can consult reviews such as by Pettersson-Yeo et al (2011) and Uhlhaas (2013), the latter showing increased and decreased connectivity and how it impacts on overall neural synchrony. Dysconnectivity is also present in other conditions involving negative symptoms, such as ADHD, where reduced dorsal caudate functional connectivity with the superior and middle PFC, and reduced putamen connectivity with the parahippocampal cortex have been identified (Hong et al, 2015). In ADHD temporal variability of functional connections appears to be associated with executive function deficits, and intrinsic dysconnectivity is linked to hyperactivity, impulsivity, and depression (Bartfield et al, 2014). Beyond the role of dysconnectivity in negative symptoms it also plays a role in regulation, as suggested by the ADHD results. To examine this role it is important to consider how negative symptoms relate to regulation.

Negative Symptoms & Regulation

As presented in the preceding chapters, regulation appears to be critical for healthy functioning, with deficient regulation resulting in for the most part adaptive hypomania progressing to mostly maladaptive mania, and also the persistent intrusion of extreme cognitive distortions, thought form alterations, and sensory perceptual experiences into the conscious and awake state (psychosis). In the case of depression and anxiety impaired regulation of excessive limbic system activity appears to be involved, and it is viable that negative symptoms might play a role in this impairment. Regulation itself seems to rely on adequate connectivity, as we noted in the "Anxiety" and "Depression" chapters. In schizophrenia and BPI there are numerous examples of dysconnectivity, as reviewed above in reference to negative symptoms. It is quite likely that patterns of dysconnectivity inherent in negative symptoms also impair or damage regulation pertaining to schizophrenia and BPI, particularly considering how extensive the problems of connectivity are involving cortical and subcortical structures, and both local and distal connections.

Research shows how dysconnectivity can impair regulation. A study by Yoon et al (2008) revealed that during a high cognitive control task, connectivity between the dorsolateral PFC and task relevant brain regions is impaired in those with schizophrenia, resulting in reduced performance. Pertaining to psychosis, those with a psychotic illness (schizophrenia spectrum or psychotic bipolar) experience disruptions across various brain networks, and in particular reduced functional connectivity within the frontoparietal control network (Baker et al, 2014). In first episode psychosis, top down (frontal, parietal, occipital) connectivity, and control of sensorimotor, basal ganglia, and limbic-visual systems is impaired, with a negative correlation apparent between efficiency of the sensorimotor system and severity of psychosis (lesser efficiency more psychosis) (Zhang et al, 2014). In bipolar disorder with psychosis there is more severe dysconnectivity, particularly between the medial thalamic nucleus and prefrontal networks (Anticevic et al, 2014).

While it is apparent that dysconnectivity is associated with negative symptoms and regulation, the nature of the relationship between these events and psychosis needs clarification. One possibility is that negative symptoms themselves result in psychosis and mania. However, regarding psychosis and negative symptoms, as we learned at the start of this chapter, there are too many differences in course of illness, symptoms, response to treatment, neurochemistry relevant to pharmacological intervention, neurobiology, neuropsychological functioning, family history, premorbid adjustment, and risk factors to support this conjecture (Arango et al, 2004; Carpenter et al, 1999; Fanous et al, 2001; Fenton & McGlashan, 1994; Horan & Blanchard, 2003; Kirpatrick et al, 2000; Kirkpatrick et al, 2001; Klemm et al, 2006; Lahti et al, 2001; Malaspina & Coleman, 2003; Pogue-Geile & Harrow, 1984; Vaiva et al, 2002). In addition, if negative symptoms in and of themselves result in positive symptoms, there would be both a tighter correlation and response pattern to interventions. The extent of negative symptoms would largely predict the degree of positive symptoms, but that is not what occurs with varying levels occurring in both schizophrenia and BPI, such as so-called positive (non-deficit) and negative (deficit) schizophrenia (Amador et al, 1999; Arango et al, 2004; Bowins,

2011; Galderisi et al, 2008; Kimhy et al, 2006; Kirkpatrick & Buchanan, 1990; Kirkpatrick et al, 2000; Peralta & Cuesta, 2004). Regarding executive function deficits, one study found that they did not actually predict jumping to conclusions distortions in psychosis, but did do so in the normal population (Langdon et al, 2014). If negative symptoms actually caused positive symptoms one would expect antipsychotics to work for negative symptoms, but the impact is minimal and involves alternative neurochemical targets than dopamine (Galletly, 2009; Goff & Coyle, 2001; Gupta & Kulhara, 2010; Heresco-Levy, 1999; Javitt, 2008; Lane et al, 2005; Uchida et al, 2011).

A couple of brief clinical case examples will help illustrate how negative and positive symptoms are not tightly related, and how intervention patterns differ. Jim is a middle-aged man who throughout his life has struggled with social relationships, both personal and at work. He described his parents as "nerdy" with few friends, who fit together well. In his childhood and teenage years he struggled to make friends, and was picked on for being "odd." During adolescence he thought it was fine to approach teenage girls and young women, slap them on the buttocks, and run away. In the present he touches female coworkers and casual contacts to give them a shoulder massage, without first asking for their permission. Despite his significant intelligence and only somewhat limited motivation, he has always worked below his capacity, largely because he was never able to navigate the social and political landscape on the job. Clearly social cognition is lacking, and if we were to directly link negative and positive symptoms, we would predict that Jim is psychotic and likely schizophrenic. However, we would be wrong, as he has never experienced psychosis, nor apparently have his parents.

Frank is a man in his late 20's, who, like Jim, suffers from social cognitive deficits. Frank does not have any sense of how to approach women beyond everyday interactions. He has no close friends as he cannot decipher intentions and respond appropriately. Despite being quite intelligent, like Jim he works below his capacity, largely due to an inability to navigate the social and political landscape on the job. There are some definite cognitive and motivational limitations, but social cognition problems are most prominent. Given that he is quite psychologically minded, we have worked on his social cognition going over appropriate responses to social scenarios during therapy sessions. He has also tested his emotion recognition online and found it to be impaired, leading him to practice recognizing facial expressions. Only very limited gains though have transpired from these interventions. Similar patterns are then present in Frank and Jim, but Frank also has pronounced delusions of persecution and reference, that respond to antipsychotics, although the social cognitive problems fail to respond to medication treatment. These examples illustrate how, of two people with similar negative symptoms, one is psychotic and the other not, an occurrence not to be expected if negative symptoms directly result in positive symptoms.

Instead of negative symptoms in and of themselves resulting in positive symptoms, what is more likely to transpire is that the neural disease process or processes causing negative symptoms via dysconnectivity also damage or impair the cognitive regulatory control processes blocking psychotic level cognitions from entering the conscious and awake state, and the conversion of hypomania to mania

(Bowins, 2008, 2011). This occurrence is in line with how the typical pattern in schizophrenia is a very long prodrome of negative symptoms, followed by the development of positive symptoms. The neural disease process/es producing negative symptoms at some point appears to damage the cognitive regulatory processes blocking extreme cognitive distortions, thought form variants, and sensory perceptual expression from the conscious and awake state (Addington & Addington, 2009; Amador et al, 1999; Arango et al, 2004; Buchanan et al, 1990; Dickinson et al, 2010; Galletly, 2009; McCullumsmith, 2004). Given the role of excessive dopamine in impaired cognitive regulatory control over psychotic level cognitions, covered in the "Psychosis" chapter, damage to this regulation likely transpires via the proximal mechanism of sustained dopamine elevations. This process might involve compensatory increases in dopamine in reaction to the extensive and severe decline in human specific cognition, based upon how dopamine can enhance cognitive flexibility and plasticity (see the "Psychosis" chapter).

Evidence supports there being major disruptions in control processes. For example, cognitive control problems pertaining to intrusive cognitions, source monitoring, and inhibitory control, have been identified in auditory verbal hallucinations (Badcock & Hugdahl, 2012). Deficient regulation over emotional processes, involving aberrant modulation of neural response during the interaction between cognitive control and emotion processing, is present as well in schizophrenia (Vercammen et al, 2012). Given that the cognitive regulatory control over psychotic level cognitions is likely continuously organized, being stronger in some people and weaker in others, there will be some range in vulnerability to the neural disease process/es underlying negative symptom damage. However, with sufficient impairment psychosis is highly likely. Regarding the possibility of psychosis causing negative symptoms, or the latter being some defensive response to psychosis as expressed by Rector et al (2005), the pattern of negative symptoms followed by positive symptoms in schizophrenia makes these perspectives untenable, and severe positive symptoms do not predict negative deficit symptoms (Kirkpatrick et al, 2001).

Negative symptoms help explain why schizophrenia emerges at different ages. Schizophrenia has been described as both a neurodevelopmental and neurodegenerative disease (Gupta & Kulhara, 2010). Human specific cognitive capacities are not fully present at birth, but instead mature over at least the first couple of decades, as likely do the cognitive regulatory control processes hypothesized to play a key role in psychosis, bipolar disorder, depression, and anxiety. Failure in the neurodevelopment of human specific cognition, and hence negative symptom onset, can thus develop over at least a couple of decades. Earlier failure might be expected to lead to worse outcomes, given the longer and more extensive impairment to human specific cognition. Supporting this possibility, brain damage in schizophrenia has been found to occur on a continuum from maximal with childhood onset, to moderate with adolescent onset, to least with adult onset (Biswas et al, 2006). When schizophrenia develops later in life it is likely the case that human specific cognitive capacities are slowly deteriorating (neurodegeneration), producing the gradual emergence of negative symptoms.

Much more rapid declines are more consistent with a dementing illness (Palmer et al, 2010). Late onset schizophrenia appears to be characterized by fewer negative symptoms than early onset schizophrenia (Brodaty et al, 1999).

The proposed model also helps explain why mania and psychosis occur together, in that when significant negative symptoms are present in bipolar disorder, both the cognitive regulatory control processes blocking the conversion of mostly adaptive hypomania to mostly maladaptive mania, and the emergence of psychosis, can be impaired. Of course, if the hypomanic defensive response to depression is not present, then there is no issue of hypomania progressing to mania. Given that hypomania is an energetic response, with increased behavioral activation and reduced behavioral inhibition (Meyer et al, 1999; Meyer et al, 2001), it is feasible that if negative symptoms are extremely severe, such that they impede behavioral activation, then the capacity for a hypomanic response to depression might be difficult to produce (Bowins, 2013). In the case of schizophrenia the continuous distribution of positive and negative symptom profiles can be explained by the model presented: When the cognitive regulatory control processes are heavily impacted with relatively limited negative symptoms, positive symptom (non-deficit) schizophrenia occurs; when the cognitive regulatory control processes are relatively spared despite pronounced negative symptoms, negative symptom (deficit) schizophrenia transpires; approximately equal negative and positive symptoms occur when damage to the cognitive regulatory control processes are more in synch with negative symptoms (Bowins, 2011).

The model presented currently remains hypothetical but it does explain several interesting phenomena, including:

- Why we seem to be prone to psychosis, but expressions in the conscious and awake state are quite rare.
- Defensive activation of psychosis in some instances as covered in the "Psychosis" chapter.
- Occurrence of both positive and negative symptom forms of schizophrenia.
- Why a long prodrome of negative symptoms precede positive symptoms in schizophrenia.
- The failure to identify an ideal animal equivalent to schizophrenia—it requires human specific cognition.
- Why hypomania shifts to mania, and the role of negative symptoms in this process.
- Why psychosis often occurs when there is mania.
- How influences such as antidepressants and other psychoactive substances, not present during the vast majority of our evolution, can induce mania and psychosis in those who are prone to it—by impairing the cognitive regulatory control processes.

The theory also suggests new approaches to treating psychosis and mania as covered in the respective chapters. Regarding treatment of negative symptoms, considering the lengthy erosion of human specific cognition, truly effective treatment interventions will likely have to focus on halting or reversing early damage to preserve human specific cognition. From a perspective of psychotherapy, it is important to appreciate that anyone with deficits to human specific cognition

might have difficulty working with the cognitive, social, and motivational demands of treatment. If there are impairments to executive functions, such as working memory, cognitive flexibility, and attention, the person will have challenges processing information, such as transference interpretations, or even working hypothesis of mental illness issues. Consequently, information might have to be parsed out in smaller units, and kept in concrete terms with more examples provided. Language might also have to be kept very basic.

Social cognitive impairments can limit a person's ability to respond appropriately to the social interaction between therapist and client, and also transform any social learning into constructive improvements in social interactions with others. More extensive role-playing is often required, with assistance provided in identifying emotions in facial expressions (facial expression recognition). Regarding motivational states, a frequent frustration encountered by therapists is not seeing clients transform therapeutic interventions into behavioral advances away from therapy. Such frustration can be diminished through an understanding of how negative amotivational symptoms play a role in this outcome, even in those not suffering from schizophrenia or severe mood disorders. Targeting specific behavioral improvements, as opposed to more general motivation, can help a client progress with behaviors outside of psychotherapy. For instance, focus on having a person engage with coworkers at lunch, instead of trying to advance socialization in general. Identifying and working with negative symptoms entails conscious awareness, both for therapist and client, of the relevant human specific cognitions and deficits that exist.

Resolving Diagnostic Confusion

The perspective presented regarding negative symptoms and their linkage to psychosis and bipolar disorder, can also help sort out the massive confusion that arises regarding the diagnosis of schizophrenia, schizoaffective, and bipolar disorder, as well as other psychotic conditions. Every practicing clinician experiences difficulty in diagnosing schizophrenia and bipolar disorder in real life settings where mixtures of symptoms are the norm. Frequently, we just put down "schizoaffective disorder" hoping that this resolves the confusion, but it actually just adds to it, and represents a default category. What is schizoaffective? It might be a combination of both schizophrenia and bipolar disorder, or a mid-point on a continuum from schizophrenia to bipolar disorder (Malhi et al, 2008). There is evidence for all three lying on a continuum (Kendler et al, 1995), but also for schizophrenia and bipolar disorder being distinct, with no real room for schizoaffective, other than perhaps a combination (Winokur et al, 1996). Smith et al (2009) found similar levels of negative symptoms in schizophrenia, schizoaffective disorder, and bipolar disorder, suggesting that negative symptoms are a crucial focal point.

Bipolar disorder consists of depression, at least at some point, and the hypomanic-manic defensive response with actual mania, at least at some point. Given that there is no evidence for hypomania being maladaptive when viewed in line with a 1-3 day expression, the real concern is mania. Defective cognitive

regulatory control processes, linked to negative symptoms and dysconnectivity, appear to facilitate the progression of hypomania to mania, as well as the emergence of psychosis in the context of mania. On the other hand, schizophrenia does not involve the hypomanic-manic defensive response to depression, or at least the progression to actual mania. Depression, though, can and frequently does occur in the context of schizophrenia, and hypomania not progressing to mania is feasible. Given that mania is not present, psychosis occurs in a non-manic context.

Negative symptoms, or more directly the neural disease process/es producing dysconnectivity that underlies these symptoms, play a key role in impairing or damaging the cognitive regulatory control processes related to psychosis, and also the conversion of hypomania to mania. In this framework the distinction between bipolar disorder and schizophrenia is clear in line with the early work of Kraepelin (1919/1971), although based on a much different model. Schizoaffective disorder has no place and is non-sensible, because there can be no such thing as a continuum directly from bipolar disorder to schizophrenia, given that the former involves mania based on the hypomanic-manic defensive response to depression, and impaired regulation over this defense. There are however continuums in terms of negative symptoms, positive symptoms, hypomania-mania, and cognitive regulatory control processes (although the latter are hypothesized to be distinct for the conversion of hypomania to mania and psychosis), explaining the overlap between these conditions. If a scenario arises where a person has psychosis in the context of mania, but at other times psychosis when there is absolutely no mania but significant negative symptoms, then both conditions can be diagnosed, but not schizoaffective disorder. By cleaning up diagnoses and dispensing with the confusing default diagnosis of schizoaffective disorder, both research and clinical efforts can be improved, and remove the discipline from charges such as schizophrenia being a failed category (Bentall, 2003).

Concluding Note

Negative symptoms are often the sleeper, being far less visible than their dramatic counterpart, positive symptoms. However, despite their lower profile they are instrumental in many conditions, such as intellectual disability, specific learning disorders, autism, and ADHD. They play a prominent role in the symptoms associated with both schizophrenia and bipolar disorder. The neural disease process/es, and resulting dysconnectivity, that produces negative symptoms appears to damage or impair, first, cognitive regulatory processes blocking the expression of extreme cognitive distortions, thought form variants, and sensory perceptual expressions in the conscious and awake state, resulting in psychosis, and second, the conversion of mostly adaptive hypomania to mostly maladaptive mania, with both forms of damage common to bipolar disorder.

References

Addington, J., & Addington, D. (2009). Three-year outcome of treatment in an early psychosis program. *Canadian Journal Of Psychiatry*, 54, 626-630.

Adler, C.M., Holland, S.K., Schmithorst, V., Wilke, M., Weiss, K.L., Pan, H., & Strakowski, S.M. (2004). Abnormal frontal white matter tracts in bipolar disorder: A diffusion tensor imaging study. *Bipolar Disorder*, 6(3), 197-203.

Amador, X.F., Kirkpatrick, B., Buchanon, R.W., Carpenter, W.T., Marcinko, L., & Yale, S.A. (1999). Stability of the diagnosis of deficit syndrome in schizophrenia. *American Journal Of Psychiatry,* 156(4), 637-639.

Ancin, I, Cabranes, J.A., Santos, J.L., Sanchez-Moria, E., & Barabash, A. (2013). Executive deficits: A continuum schizophrenia-bipolar disorder or specific to schizophrenia? *Psychiatry Research*, 47(11), 1564-1571.

Anticevic, A., Brumbaugh, M.S., Winkler, A.M., Lombardo, L.E., Barett, J., & Corlett, P.R. (2013). Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. *Biological Psychiatry*, 73(6), 565-573.

Anticevic, A., Yang, G., Savic, A., Murray, J.D., Cole, M.W., Repovs, G., et al. (2014). Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis. *Schizophrenia Bulletin*, 40(6), 1227-1243.

Arango, C., Buchanan, R., Kirkpatrick, B., & Carpenter, W. (2004). The deficit syndrome in schizophrenia: Implications for the treatment of negative symptoms. *European Psychiatry*, 19, 21-26.

Argyelan, M., Ikuta, T., DeRosse, P., Braga, R.J., Burdick, K.E., John, M., et al. (2014). Resting-state fMRI connectivity impairment in schizophrenia and bipolar disorder. *Schizophrenia Bulletin*, 40(1), 100-110.

Arts, B., Jabben, N., Krabbendam, L., & Van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar disorder patients and their first-degree relatives. *Psychological Medicine*, 38(6), 771-785.

Ashby, F.G., Isen, A.M., & Turken, U. (1999). A neuropsychological theory of positive affect and its influence on cognition. *Psychological Review*, 106(3), 529-550.

Atkins, P. (2007). *Four Laws That Drive The Universe*. Oxford, England; Oxford University Press.

Atre-Vaidya, N., Taylor, M.A., Seidenberg, M., Reed, R., Perrine, A., & Glick-Oberwise, F. (1998). Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. *Neuropsychiatry & Neuropsychology Behavioral Neurology*, 11(3), 120-126.

Badcock, J.C., & Hugdahl, K. (2012). Cognitive mechanisms of auditory verbal hallucinations in psychotic and non-psychotic groups. *Neuroscience & Biobehavioral Reviews*, 36, 431-438.

Baker, J.T., Holmes, A.J., Masters, G.A., Yeo, B.T., Krienen, F., Buckner, R.L., & Ongur, D. (2014). Disruption of cortical association networks in schizophrenia and psychotic bipolar disorder. *JAMA Psychiatry*, 71(2), 109-118.

Ballmaier, M., Schlagenhauf, F., Toga, A.W., Gallinat, J., Koslowski, M., Zoli, M., et al. (2008). Regional patterns and clinical correlates of basal ganglia morphology in non-medicated schizophrenia. *Schizophrenia Research*, 106(2-3), 140-147.

Bartfeld, P., Petroni, A., Baez, S., Urquina, H., Sigman, M., Cetkovich, M., et al. (2014). Fiunctional connectivity and temporal variability of brain connections in adults with attention deficit/hyperactivity disorder and bipolar disorder. *Neuropsychobiology*, 69(2), 65-75.

Bediou, B., Asri, F., Brunelin, J., Krolak-Salmon, P., D'Amato, T., Saoud, M., & Tazi, I. (2007). Emotion recognition and genetic vulnerability to schizophrenia. *British Journal Of Psychiatry*, 191, 126-130.

Bemporad, J.R. (1991). Dementia praecox as a failure of neoteny. *Theoretical Medicine*, 12, 45-51.

Bentall, R.P. (2003). *Madness Explained: Psychosis And Human Nature*. London: Penguin.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., et al. (2000). Neuropsychology of first-episode schizophrenia: Initial characterization and clinical correlates. *American Journal Of Psychiatry*, 157, 549-559.

Biswas, P., Malhorta, S., Malhotra, A., & Gupta, N. (2006). Comparative study of neuropsychological correlates in schizophrenia with onset in childhood, adolescence and adulthood. *European Child & Adolescent Psychiatry*, 15(6), 360-366.

Blanchard, J.J., Bellack, A.S., & Mueser, K.T. (1994), Affective and social-behavioral correlates of physical and social anhedonia in schizophrenia. *Journal Of Abnormal Psychology*, 103(4), 719-728.

Bowins, B. (2008). Hypomania: A depressive inhibition override defense mechanism. *Journal of Affective Disorders*, 109, 221-232.

Bowins, B.E (2011). A cognitive regulatory control model of schizophrenia. *Brain Research Bulletin*, 85 36-41.

Bowins, B.E. (2013). Cognitive Regulatory Control Therapies. *American Journal Of Psychotherapy*, (67(3), 215-236.

Brandt, C.L., Eichele, T., Melle, I., Sundet, K., Server, A., Agartz, I., et al. (2014). Working memory networks and activation patterns in schizophrenia and bipolar disorder: Comparison with healthy controls. *British Journal Of Psychiatry*, 204, 290-298.

Brodaty, H., Sachdev, P., Rose, N., Rylands, K., & Prenter, L. (1999). Schizophrenia with onset after age 50 years. I: Phenomenology and risk factors. *British Journal Of Psychiatry*, 175, 410-415.

Buchanan, R.W., Kirkpatrick, B., Heinrichs, R.W., & Carpenter, W.T. (1990). Clinical correlates of the deficit syndrome in schizophrenia. *American Journal Of Psychiatry*, 147, 290-294.

Burns, J.K. (2009). Reconciling 'the new epidemiology' with an evolutionary genetic basis for schizophrenia. *Medical Hypothesis*, 72, 353-358.

Cacioppo, S., & Cacioppo, J.T. (2012). Decoding the invisible forces of social connections. *Frontiers Of Integrated Neuroscience*, 25(6), 51-59.

Carpenter, W., Arango, C., Buchanan, R., & Kirkpatrick, B. (1999). Deficit psychopathology and a paradigm shift in schizophrenic research. *Biological Psychiatry*, 46, 352-360.

Carpenter, W.T., Heinrichs, D.W., & Wagman, A.M. (1988). Deficit and nondeficit forms of schizophrenia: The concept. *American Journal Of Psychiatry*, 145, 578-583.

Collette, F., Van der Linden, M., & Laureys, S. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Human Brain Mapping*, 25(4), 409-423.

Collin, D., De Reus, M.A., Cahn, W., Hulshoff-Pol, H.E., Kahn, R.S., & Van Den Heuvel, M.P. (2013), Disturbed grey matter coupling in schizophrenia. *European Neuropsychopharmacology*, 23(1), 46-54.

Combs, D.R., Finn, J.A., Wohlfahrt, W., Penn, D.L., & Basso, M.R. (2013). Social cognition and social functioning in nonclinical paranoia. *Cognitive Neuropsychiatry*, 18(6), 531-548.

Coryell, W. (1997). Do psychotic, minor, and intermittent depressive disorders exist on a continuum. *Journal Of Affective Disorders*, 45(1-2), 75-83.

Daly, M.P., Afroz, S., & Walder, D.J. (2012). Schizotypal traits and neurocognitive functioning among nonclinical young adults. *Psychiatry Research*, 30, 635-640.

Darwin, C. (1858/1859). *On The Origin Of Species*. New York: Signet Classic.

De Jong, J.J., De Gelder, B., & Hodiamont, P.P. (2013). Sensory processing, neurocognition, and social cognition in schizophrenia: Towards a cohesive cognitive model. *Schizophrenia Research*, 146(1-3), 209-216.

Deutsch, D. (1998). *The Fabric Of Reality*. London, England; Penguin Books.

Dickinson, D., Tenhula, W., Morris, S., Brown, C., Peer, J., Spencer, K., et al. (2010). A randomized controlled trial of computer-assisted cognitive remediation for schizophrenia. *American Journal Of Psychiatry*, 167, 170-180.

Di Nicola, M., De Risio, L., Battaglia, C., Camardese, G., Tedeschi, D, Mazza, M., et al. (2013). Reduced hedonic capacity in euthymic bipolar subjects: A trait-like feature? *Journal Of Affective Disorders*, 147(1-3), 446-450.

Eisenberg, D.P., & Berman, K.F. (2010). Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology*, 35(1), 258-277.

Elvevag, B., & Goldberg, T.E. (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Critical Review Of Neurobiology*, 14, 1-21.

Fanous, A., Gardner, C., Walsh, D., & Kendler, K. (2001). Relationship between positive and negative symptoms of schizophrenia and schizoptypal symptoms in nonpsychotic relatives. *Archives Of General Psychiatry*, 58(7), 669-673.

Fenton, W.S., & McGlashan, T.H. (1994). Antecedents, symptom progression, and long-term outcome in the deficit syndrome in schizophrenia. *American Journal Of Psychiatry*, 151, 351-356.

Fett, A.K., Viechtbauer, W., Dominguez, M.D., Penn, D.L., Van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Review*, 35(3), 573-588.

Fiszdon, J.M., Richardson, R., Greig, T., & Bell, M.D. (2007). A comparison of basic and social cognition between schizophrenia and schizoaffective disorder. *Schizophrenia Research*, 91, 117-121.

Galderisi, S., Quarantelli, M., Volpe, U., Mucci, A., Cassano, G., Invernizzi, G., et al. (2008). Patterns of structural MRI abnormalities in deficit and nondeficit schizophrenia. *Schizophrenia Bulletin*, 34(2), 393-401.

Galletly, C. (2009). Recent advances in treating cognitive impairment in schizophrenia. *Psychopharmacology*, 202, 1302-1309.

Glantz, K., & Pearce, J. (1989). *Exiles From Eden: Psychotherapy From An Evolutionary Perspective*. New York: W.W. Norton & Company.

Godefroy, O., Cabaret, M., & Petit-Chenal, V., (1999). Control function of the frontal lobes. Modularity of the central-supervisory system? *Cortex*, 121(1), 65-94.

Goff, D.C., & Coyle, J.T. (2001). The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *American Journal Of Psychiatry*, 158(9), 1367-1377.

Goleman, D. (1995). *Emotional Intelligence*. New York: Bantam Books.

Gross, R.G., & Grossman, M. (2010). Executive resources. *Continuum*, 16(4), 140-152.

Guo, S., Palaniyappan, L., Yang, B., Liu, Z., Xue, Z., & Feng, J. (2014). Anatomical distance affects functional connectivity in patients with schizophrenia and their siblings. *Schizophrenia Bulletin*, 40(2), 449-459.

Gupta, S., & Kulhara, P. (2010). What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or combination of both. A critical analysis. Indian *Journal Of Psychiatry*, 52(1), 21-27.

Harvey, P.D. (2011). Mood symptoms, cognition, and everyday functioning: In major depression, bipolar disorder, and schizophrenia. Innovations In Clinical *Neuroscience*, 8(10), 14-18.

Helldin, L., Kane, J.M., Karilampi, U., Norlander, T., & Archer, T. (2006). Remission and cognitive ability in a cohort of patients with schizophrenia. *Journal Of Psychiatry Research*, 40, 738-745.

Heresco-Levy, U., Javitt, D.C., Ermilov, M., Mordel, C., Silipo, G., & Lichenstein, M. (1999). Efficacy of high dose glycine in the treatment of enduring negative symptoms of schizophrenia. *Archives Of General Psychiatry*, 56(1), 29-36.

Hong, S.B., Harrison, B.J., Fornito, A., Sohn, C.H., Song, I.C., & Kim, J.W. (2015). Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder. *Journal Of Psychiatry & Neuroscience*, 40(1), 46-57.

Horan, W.P., & Blanchard, J.J. (2003). Neurocognitive, social, and emotional dysfunction in deficit syndrome schizophrenia. *Schizophrenia Research*, 65, 125-137.

Ivleva (a), E.I., Morris, D.W., Osuji, J., Moates, A.F., Carmody, T.J., Thaker, G.K., et al. (2012). Cognitive endophenotypes of psychosis within dimension and diagnosis. *Psychiatry Research*, 196(1), 38-44.

Ivleva (b), E.I., Shohamy, D., Mihalakos, P., Morris, D.W., Carmody, T., & Tamminga, C.A. (2012). Memory generalization is selectively altered in the psychosis dimension. *Schizophrenia Research*, 138(1), 74-80.

Javitt, D.C. (2008). Glycine transport inhibitors and the treatment of schizophrenia. *Biological Psychiatry*, 63, 6-8.

Johnson, M.K., McMahon, R.P., Robinson, B.M., Harvey, A.N., Hahn, B., Leonard, C.J., et al. (2013). The relationship between working memory capacity and broad measures of cognitive ability in healthy adults and people with schizophrenia. *Neuropsychology*, 27(2), 220-229.

Kaiser, S., Heekeren, K., & Simon, J.J. (2011). The negative symptoms of schizophrenia: Category or continuum? *Psychopathology*, 44(6), 345-353.

Keefe, R.S., & Fenton, W.S. (2007). How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophrenia Bulletin*, 33, 912-920.

Kendler, K.S., Neale, M.C., & Walsh, D. (1995). Evaluating the spectrum concept of schizophrenia in the Roscommon family study. *American Journal Of Psychiatry*, 152(5), 749-754.

Kimhy, D., Yale, S., Goetz, R., McFarr, L., & Malaspina, D. (2006). The factorial structure of the schedule for the deficit syndrome in schizophrenia. *Schizophrenia Bulletin*, 32(2), 274-278.

Kirkpatrick, B., & Buchanan, R.W. (1990). The neural basis of the deficit syndrome of schizophrenia. *The Journal Of Nervous And Mental Disease*, 178, 545-555.

Kirkpatrick, B., Buchanan, R.W., McKenney, P.D., Alpha, L.D., & Carpenter, W.T. (1989). The schedule for the deficit syndrome: An instrument for research in schizophrenia. *Psychiatry Research*, 30(2), 119-123.

Kirkpatrick, B., Buchanan, R.W., Ross, D.E., & Carpenter, W.T. (2001). A separate disease within the syndrome of schizophrenia. *Archives Of General Psychiatry*, 58, 165-171.

Kirkpatrick, B., Ross, D.E., Walsh, D., Karkowski, L, & Kendler, K.S. (2000). Family characteristics of deficit and nondeficit in schizophrenia in roscommon family study. *Schizophrenia Research*, 45, 57-64.

Klemm, S., Schmidt, B., Knappe, S., & Blanz, B. (2006). Impaired working speed and executive functions as frontal lobe dysfunctions in young first-degree relatives of schizophrenic patients. *European Child & Adolescent Psychiatry*, 15, 400-408.

Knochel, C., Stablein, M., Storchak, H., Reinke, B., Jurcoane, A., Prvulovic, D., et al. (2014). Multimodal assessments of the hippocampal formation in schizophrenia and bipolar disorder: Evidence from neurobehavioral measures and functional and structural MRI. *Neuroimaging Clinics*, 23(6), 134-144.

Kraepelin, E. (1919/1971). *Dementia Praecox And Paraphrenia*. New York: Krieger.

Kulhara, K., & Chandiramani, T. (1990). Positive and negative subtypes of schizophrenia. A follow-up study from India. *Schizophrenia Research*, 3(2), 107-116.

Kumar, J., Iwabucchi, S., Oowise, S., Balain, V., Palaniyappan, L., & Liddle, P.F. (2014). Shared white-matter dysconnectivity in schizophrenia and bipolar disorder with psychosis. *Psychological Medicine*, 4, 1-12.

Kuswanto, C.N., Sum, M.Y., & Sim, K. (2013). Neurocognitive functioning in schizophrenia and bipolar disorder: Clarifying concepts of diagnostic dichotomy vs. continuum. *Frontiers In Psychiatry*, 5(4), 162-169.

Lahti, A.C., Holocomb, H.H., Medoff, D.R., Weiler, M.A., Tamminga, C.A., & Carpenter, W.T. (2001). Abnormal patterns of regional cerebral blood flow in schizophrenia with primary negative symptoms during an auditory recognition task. *American Journal Of Psychiatry*, 158, 1797-1808.

Lane, H., Chang, Y., Liu, Y., Chiu, C., & Guochan, T. (2005). Sarcosine or d-serine add-on treatment for acute exacerbation of schizophrenia. *Archives Of General Psychiatry*, 62(11), 1196-1204.

Langdon, R., Still, M., Connors, M., Ward, P., & Catts, S. (2014). Jumping to delusions in early psychosis. *Cognitive Neuropsychiatry*, 19(3), 241-256.

Lucas, S., Fitzgerald, D., Redoblado-Hodge, A., Anderson, J., Sanbrook, M., Harris, A., et al. (2004). Neuropsychological correlates of symptom profiles in first episode schizophrenia. *Schizophrenia Research*, 71, 323-330.

Mahurin, R.K., Velligan, D.I., & Miller, A.L. (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: A symptom subtype analysis. *Psychiatry Research*, 79, 139-149.

Malaspina, D., & Coleman, D. (2003). Olfaction and social drive in schizophrenia. *Archives Of General Psychiatry*, 60, 578-584.

Malhi, G.S., Green, M., Fagiolini, A., Peselow, E.D., & Kumari, V. (2008). Schizoaffective disorder: Diagnostic issues and future recommendations. *Bipolar Disorder*, 10(1-2), 215-230.

Mamah, D., Barch, D.M., & Repovs, G. (2013). Resting state functional connectivity of five neural networks in bipolar disorder and schizophrenia. *Journal Of Affective Disorders*, 150(2), 601-609.

Mateer, C.A. (1999). Executive function disorders: Rehabilitation challenges and strategies. *Seminars In Clinical Neuropsychiatry*, 4(1), 50-59.

McCullumsmith, R.E., Clinton, S.M., & Meador-Woodruff, J.H. (2004). Schizophrenia as a disorder of neuroplasticity. *International Review Of Neurobiology*, 59, 19-45.

Meda, S.A., Gill, A., Stevens, M.C., Lorenzoni, R.P., Glahn, D.C., Calhoun, V.D., Sweeney, J.A., et al. (2012). Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. *Biological Psychiatry*, 71(1), 881-889.

Meyer, B., Johnson, S.L., & Carver, C.S. (1999). Exploring behavioral activation and inhibition sensitivities among college students at risk for bipolar spectrum symptomatology. *Journal Of Psychopathology & Behavioral Assessment*, 21, 275-292.

Meyer, B., Johnson, S.L., & Winters, R. (2001). Responsiveness to threat and incentive in bipolar disorder: Relations of the BIS/BAS scales with symptoms. *Journal Of Psychopathology & Behavioral Assessment*, 23, 133-143.

Miyake, A., Friedman, N.P., & Emerson, M.J. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology*, 41(1), 49-100.

Monchi, O., Petrides, M., & Strafella, A.P. (2006). Functional role of the basal ganglia in the planning and execution of actions. *Annuals Of Neurology*, 59(2), 257-264.

Morice, R., & Delahunty, A. (1996). Frontal/executive impairments in schizophrenia. *Schizophrenia Bulletin*, 22, 125-137.

Nieto, R.G., & Castellanos, F.X. (2011). A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and bipolar disorder. *Journal Of Clinical Child & Adolescence Psychology*, 40(2), 266-280.

Oades, R.D. (1998). Frontal, temporal and lateralized brain function in children with attention-deficit hyperactivity disorder: A psychophysiological and neuropsychological viewpoint on development, *Behavioral Brain Research*, 94(1), 83-95.

Owen, M.J. (2012). Intellectual disability and major psychiatric disorders: A continuum of neurodevelopmental causality. *British Journal Of Psychiatry*, 200(4), 268-269.

Palmer, B.W., Loughran. C.I., & Meeks, T.W. (2010). Cognitive impairment among older adults with late-life schizophrenia or bipolar disorder. *Continuum*, 16(2), 135-152.

Pavlus, J. (2012). Machines of the infinite. *Scientific American*, September, 67-71.

Peralta, V., & Cuesta, M.J. (2004). The deficit syndrome of the psychotic illness: A clinical and nosological study. *European Archives Of Psychiatry & Clinical Neuroscience*, 254, 165-171.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: Where are we now? *Neuroscience & Biobehavioral Reviews*, 35(5), 1110-1124.

Pogue-Gelle, M., & Harrow, M. (1984). Negative and positive symptoms in schizophrenia and depression: A follow-up. *Schizophrenia Bulletin*, 10(3), 371-387.

Purper-Ouakil, D., & Franc, N. (2011). Emotional dysfunction in attention deficit hyperactivity disorder. *Archives De Pediatrie*, 18(6), 679-685.

Rapp, A.M., Langohr, K., Mutschler, D.E., & Wild, B. (2014). Irony and proverb comprehension in schizophrenia: Do female patients "dislike" ironic remarks? *Schizophrenia Research & Treatment*, 84, 10-18.

Rector, N.A., Beck, A.T., & Stolar, N. (2005). The negative symptoms of schizophrenia: A cognitive perspective. *Canadian Journal Of Psychiatry*, 50(5), 247-255.

Reichenberg, A., Caspi, A, Harrington, H., Houts, R., Keefe, R., Murray, R., et al. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal Of Psychiatry*, 167, 160-169.

Rossi, A., Daneluzzo, E., Mattei, P., Bustini, M., Casacchia, M., & Stratta, P. (1997). Wisconsin card sorting test and Stroop test performances in schizophrenia: A shared construct. *Neuroscience Letters*, 226, 87-90.

Sharma, A., Weisbrod, M., & Bender, S. (2013). Connectivity and local activity within the fronto-posterior brain network in schizophrenia. *Supplement Clinical Neurophysiology*, 62, 181-196.

Siebenhuhner, F., Weiss, S.A., Coppola, R., Weinberger, D.R., & Bassett, D.S. (2013). Intra- and inter-frequency brain network structure in health and schizophrenia. *Plos One*, 8(8), e72351.

Simonsen, C., Sundet, K., & Vaskinn, A. (2008). Neurocognitive profiles in bipolar I and bipolar II disorder: Differences in pattern and magnitude of dysfunction. *Bipolar Disorder*, 10, 245-255.

Skudlarski, P., Schretlen, D.J., Thaker, G.K., Stevens, M.C., Keshavan, M.S., Sweeney, J.A., et al. (2013). Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. *American Journal Of Psychiatry*, 170(8), 886-898.

Smith, M.J., Barch, D.M., & Csernansky, J.G. (2009). Bridging the gap between schizophrenia and psychotic mood disorders: Relating neurocognitive deficits to psychopathology. *Schizophrenia Research*, 107(1), 69-75.

Smith, E.E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology*, 33(1), 5-42.

Stekelenburg, J.J., Maes, J.P., Van Gool, A.R., Sitskoorn, M., & Vroomen, J. (2013). Deficient multisensory integration in schizophrenia: An event-related potential study. *Schizophrenia Research*, 147(2-3), 253-261.

Uchida, H., Takeuchi, H., Graff-Guerrero, Suzuki, T., Watanabe, K., & Mamo, D.C. (2011). Dopamine D2 receptor occupancy and clinical effects: A systematic review and pooled analysis. *Journal Of Clinical Psychopharmacology*, 31(4), 497-502.

Uhlhaas, P.J. (2013). Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. *Current Opinions In Neurobiology*, 23(2), 283-290.

Vaiva, G., Cottencin, O., & Llorca, P.M. (2002). Regional cerebral blood flow in deficit/nondeficit types of schizophrenia according to SDS criteria. *Progress In Neuro-psychophathology*, 26, 481-485.

Vercammen, A., Morris, R., Green, M.J., Lenroot, R., Kulkarni, J., Carr, V.J., et al. (2012). Reduced neural activity of the prefrontal cognitive control circuitry during response inhibition to negative words in people with schizophrenia. *Journal Of Psychiatry & Neuroscience*, 37(6), 379-388.

Volkmar, F.R., & Wolf, J.M. (2013). When children with autism become adults. *World Psychiatry*, 12(1), 78-80.

Waltereit, R., Banaschewski, T., Meyer-Lindenberg, A., & Poustka, L. (2014). Interaction of neurodevelopmental pathways and synaptic plasticity in mental retardation, autistic spectrum disorder and schizophrenia: Implication for psychiatry. *World Journal Of Biological Psychiatry*, 15(7), 507-516.

Winokur, G., Monahan, P., Coryell, W., & Zimmerman, M. (1996). Schizophrenia and affective disorder-distinct entities or continuum?: An analysis based on a prospective 6-year follow-up. *Comprehensive Psychiatry*, 37(2), 77-87.

Yoon, J.H., Minzenberg, M.J., Ursu, S., Ryan-Walter, B.S., Wendelken, C., Ragland, J.D., & Carter, C.S. (2008). Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: Relationship with impaired cognition, behavioral disorganization, and global function. *American Journal Of Psychiatry*, 165(8), 1006-1014.

Zhang, R., Wei, Q., Kang, Z., Zalesky, A., Li, M., Xu, Y., et al. (2014). Disrupted brain anatomical connectivity in medication-naïve patients with first-episode schizophrenia. *Brain Structure & Function*, 22, 50-57.