6 The evolutionary genetics of the creativity–psychosis connection

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Why is it that all those who have become eminent in philosophy or politics or poetry or the arts are clearly melancholics?

– Aristotle

Nothing in biology makes sense except in the light of evolution.

Dobzhansky (1973)

Introduction

Schizophrenia, a debilitating mental illness affecting roughly 1 percent of the population worldwide, is widely accepted as being highly genetically influenced (Cardno *et al.*, 1999; Gershon *et al.*, 1988; Kendler and Diehl, 1993). Schizophrenia is often marked by distortions of reality, disorganized thought, emotional blunting, and/or social isolation that may interfere with optimal functioning (Cornblatt *et al.*, 2012). Schizophrenia may be associated with creativity, although research findings are mixed (e.g., Andreasen, 2011; Kyaga *et al.*, 2013). Evidence also points to adverse effects on fertility and reproductive success among (particularly) males with schizophrenia (Svensson *et al.* 2007), in part accounted for by marital status (McCabe *et al.*, 2009), suggesting potential biological and social influences. Collectively, this raises an intriguing potential evolutionary puzzle: *How does schizophrenia persist in the population at a stable prevalence rate too high to be explained by simple random mutation?* (Doi *et al.*, 2009; see Del Giudice *et al.*, 2010). Among various hypotheses, including in the context of the emerging field of evolutionary epidemiology, schizophrenia may represent "one extreme of a sexually selected fitness factor" (Shaner *et al.*, 2004).

One possibility, which we explore in this chapter, is that schizophrenia remains in the human population (in part via the gene pool) because of shared genetic linkages to creativity (Andreasen, 2011; Carson, 2011), with acknowledgement of likely concurrent environmental (e.g., epigenetic) influences. Available evidence – particularly from twin

studies – suggests that both creativity and schizophrenia have a heritable basis (Barron and Parisi, 1977; Vinkhuyzen *et al.*, 2009). Moreover, schizotypal thinking is often viewed as sharing features with creative thought, such as cognitive flexibility and divergent thinking via unusual but meaningful associations. These commonalities, coupled with the observed heritability of both constructs, suggest that there may be genetic factors common to both creativity and schizophrenia. Such genetic factors may be expressed along a continuum and thus vary with respect to serving protective or risk functions. Moreover, there may be genetic and environmental influences that discourage the expression of severe forms of schizophrenia (and other mental illnesses), whereby the results of unusual thought processes may be guided by "executive control" over these thoughts, so that they are put to their most productive use.

As a preliminary, we note that the general question of the relationship between creativity and mental health concerns (including schizophrenia) remains *highly* contentious, with some arguing for strong links (e.g., Andreasen, 1987; Jamison, 1993; Kottler, 2005; Ludwig, 1995; Nettle, 2001), others for basically no relation (e.g., Sawyer, 2006; Weisberg, 2006), and others occupying either a middle ground (Eysenck, 1993; Kyaga *et al.*, 2011, 2013; Simonton, 1994) or focusing on pointing out significant methodological and conceptual limitations in much research to date (e.g., Schlesinger, 2009; Silvia and Kaufman, 2011). Many aspects of this debate are explored throughout this volume, and we will not attempt to resolve it in this chapter. Here we entertain the possibility that there may be overlap in some aspects of creativity and psychosis – particularly thought patterns and genetic links – and we explore the genetic evidence bearing on this possible connection, as well as the implications of this evidence for our thinking about the relation between mental illness and creativity.

Specifically, in this chapter, we cautiously explore an evolutionary genetics approach in attempting to understand the possible connection between schizophrenia and creativity. We first discuss some general perspectives on the evolutionary persistence of genes associated with schizophrenia, emphasizing complex *polygenic* influences (i.e., the idea that schizophrenia and other mental disorders reflect an inevitable mutational load on the thousands of genes underlying human behavior – see Keller and Miller, 2006), together with environmental influences. At a finer grain, we then detail some of the specific genetic factors that have been implicated in schizophrenia spectrum disorders and in creativity. We next explore the nature of the association between creativity and mental illnesses (particularly schizophrenic spectrum disorders), in terms of shared cognitive processes and mechanisms, as well as potential genetic

linkages. Finally, we close by noting that, while this research converges onto a more or less theoretically coherent gene's-eye perspective linking psychosis and creativity, its explanatory power may ultimately be limited, particularly when applied to understanding very high levels of creative achievement.

Perspectives on the evolutionary persistence of schizophrenia

In line with a dimensional model (Meehl, 1962, 1990), there is increasing evidence that psychotic and psychotic-like symptoms and presentation (associated with schizophrenia) fall along a continuum spanning the non-clinical (e.g., schizotypy and psychotic-like experiences, or PLEs) and the clinical (e.g., hallucinations; schizophrenia) ranges (e.g., Daly *et al*., 2012; Walder, Statucka *et al*., 2012). The generally adverse impact of schizophrenia across various functional domains together with evidence of reduced fecundity (e.g., McGrath *et al*., 1999) and high rates of the non-clinical phenotype collectively render the relatively stable, cross-cultural persistence of schizophrenia in the population an evolutionary puzzle.

Despite initial excitement in the field about the possibility of identifying major specific gene effects, recent escalating evidence instead suggests schizophrenia involves complex (i.e., diagnostically non-specific) polygenic influences (see Walder *et al*., 2012). Some have argued that there may be shared genetic variation between illness and non-clinical psychotic-like symptom expression, and that the relatively high prevalence of the non-clinical phenotype may "mask" identification of these critical genes when comparing diagnostic groups – and that such genes may carry an evolutionary advantage (Kelleher *et al*., 2010). This perspective argues for the import of conducting studies more closely examining genetic and behavioral variation among individuals in the general population who experience PLEs, towards uncovering schizophrenia etiology (see Daly *et al*., 2012; Walder, Statucka *et al*., 2012). For example, some traits may have an optimal level of expression that is advantageous within the general population, beyond which the trait has adverse consequences for the individual.

The question regarding what processes maintain the persistence of high heritable variation in relatively disadvantageous traits – such as schizotypy (and in its extreme form, schizophrenia) – in the general population remains a universal challenge across the domains of Darwinian psychiatry, psychiatric genetics, and evolutionary genetics (Keller and Miller, 2006). To date, several evolutionary theories have been proposed

using the Darwinian paradigm of selective advantage as a frame to account for evolutionary persistence of psychosis (see review by Kelleher *et al.*, 2010). For instance, Crow's (1997) "speciation hypothesis" argued that language developed at the price of psychosis. Burns' (2004) "costly-by-product" hypothesis posited that schizophrenia emerged as a by-product of social cognition, and argued for a paradigm shift including a "new philosophy of mind" towards an integrated "socio-neurologically" based understanding of mental disorders. Nesse's (2004) "cliff-edge" fitness theory contended that particular traits enhance fitness until a critical threshold, beyond which fitness diminishes. Dodgson and Gordon (2009) suggested that some hallucinations are evolutionary byproducts of cognitive threat-detection systems reflecting an evolutionary bias towards the propagation of genes that promote false positives over false negatives (e.g., hypervigilance hallucinations) among a few members of society; while at times disadvantageous at the individual level, this may be advantageous at the group level. In yet another view, Crespi and Badcock (2008a, 2008b; see also Del Giudice *et al.*, 2010) hypothesized that psychotic spectrum presentations (as with the autism spectrum) represent pathological extremes of individual differences in the cognitive dimensions defining the human "social brain." They emphasized the role of a diametrical genetic process underlying psychosis; namely, the conflict between maternally and paternally expressed imprinted genes. Specifically, Crespi and Badcock argued that psychosis is characterized by overexpression of maternally expressed genes, a view in line with the kinship theory of genomic imprinting (Burt and Trivers, 2006), which represents an evolutionary-genetic extension of kin selection and parent-offspring conflict models, whereby imprinted genes contribute (albeit not exclusively) to the origin of psychosis as well as to individual variation in schizotypy. In this way, variability in genetic sequences and epigenetic patterns of imprinting at the same genetic loci may underlie heritable individual differences.

Sexual selection through mate choice, a perspective most closely associated with Miller and colleagues (see Geher and Kaufman, 2011; Miller, 2001), represents another broad, evolution-based hypothesis accounting for the persistence of psychosis-proneness in the human gene pool. According to Miller, our more recently evolved capacities for creativity (e.g., art, music, humor, language, and so on) are analogous to the peacock's ornate tail or the lion's mane, which do not serve any function directly relevant to the organism's survival; rather, they serve the function of attracting mates by acting as fitness indicators – revealing "good genes" and "good parent" traits. (Of course, it is now well known that genes are not uniformly "good" or "bad," as the influence of genes depends

on gene expression, which is in part contingent on neurobiological and environmental context.) In this view, individuals who can demonstrate verbal fluency, divergent thinking, and looseness of associations in a productive, meaningful way demonstrate that they have other fitness-enhancing protective factors that support such displays of creativity. Some researchers argue that schizophrenia, on the other hand, represents the low-fitness extreme of cognitive processes that are normally distributed in the general population and are associated with creative production (Shaner et al., 2008). As detailed by Del Giudice et al. (2010), some have posited that moderate schizotypy in the absence of severe mental disorder may carry a reproductive advantage beyond the potential "costs" that may accompany subsequent illness (Nettle, 2001). Specifically, the benefits of positive (versus negative) schizotypy arguably are accounted for by their association with creativity, which may enhance attractiveness and courtship success. Indeed, some research has found a higher number of sexual partners among artists (Clegg et al., 2011; Nettle and Clegg, 2006), with higher levels of mating success among creative individuals mediated by milder forms of schizophrenia. A more recent study also found that schizotypy was indirectly related to short-term mating success (through engagement in creative activity), although the findings only held for males (Beaussart et al., 2012).

There has been healthy debate about these hypotheses. While some researchers claim that there tends to be an association between schizotypy and creativity (e.g., Batey and Furnham, 2008), others argue that general intelligence and openness to experience serve as better predictors of creativity than do schizotypal traits (Miller and Tal, 2007). Thus, in line with Shaner et al.'s (2004, 2008) consideration of psychotic spectrum disorders as a disadvantageous extreme of a sexually selected fitness indicator, schizotypal traits hold potential for both maximizing mating success while also increasing the risk for psychosis, rendering high positive schizotypy a high-risk strategy that is expected to be found among males more than females. This dynamic would help account for the continued propagation of genes associated with schizophrenia, despite some relative disadvantages, over the course of human evolution.

Notably, Miller (2010) recently challenged equilibrium models like fitness neutrality, balancing selection, and pleiotropic mutations for understanding the genetic variation of traits, arguing that human traits are unlikely to have been at evolutionary equilibrium for the past several hundred generations. Miller posits the need for a novel evolutionary genetics model that appreciates the value of ongoing post-Pleistocene human evolution characterized by strong selective sweeps (i.e., relatively rapid increases in frequency of new fitness-increasing alleles) due to factors

such as increased population density (Hawks *et al*., 2007) and more selective assortative mating (Miller, 2001). Miller and colleagues highlight, at the molecular genetics level, the potential role of overall mutation load (Keller and Miller, 2006), as opposed to the more traditionally considered allelic variants targeted in genome-wide association studies (or GWAS). At the neurogenic level, they point to overall mutation load as influencing neurodevelopmental stability (Prokosch *et al*., 2005), versus particular allele effects on specific cortical regions, neurotransmitter systems, or fiber tracts. This perspective shows promise in light of increasing evidence of complex, polygenic influences in the etiology of a range of psychiatric disorders, including schizophrenia, as opposed to previously considered major specific gene effects – and the absence of convergence in identifying particular risk alleles (e.g., in GWAS studies). At the psychometric level, Miller argues for consideration of a hierarchical structure of reliably measured psychological traits that supersedes aspects of psychological functioning such as cognition, emotion, motivation, and consciousness. Finally, at the sociological level, he points out that mutation load and selection are relevant to explaining human psychodiversity. In sum, while Miller seems to advocate for an evolutionary genetics approach, he offers caution with an eye on the potential limitations of existing evolutionary genetics models and their far-reaching potential implications, which need to be carefully considered.

Thus, all told, researchers have postulated a diverse and sophisticated set of perspectives and mechanisms detailing how the evolutionary persistence of mental illnesses like schizophrenia might be explained. These explanations are not mutually exclusive, but they remain the subject of vigorous debate and empirical analysis, extending over a range of methodologies. Notably, common to many of the explanations is a link between creative and psychotic thought patterns, whose positive benefits may outweigh or at least mitigate the obvious negative effects of a psychotic disorder like schizophrenia. With this set of evolutionary genetic principles in mind, we next turn to empirical findings on specific genes associated with schizophrenic spectrum disorders, and then to genes associated with creative thought.

Genes associated with schizophrenia spectrum disorders

In line with the diathesis-stress model of schizophrenia (see Walker and Diforio, 1997; Walker *et al*., 2004), family and twin studies have demonstrated upwards of a ten-fold increased risk of developing a psychotic disorder compared with the general population (Cardno and Gottesman, 2000). As reviewed by Walder, Ospina *et al*. (2012), however, the precise

genetic contributions to psychosis remain contentious. Despite recent literature on candidate gene approaches and GWAS initially seeming to suggest small to moderate gene effects in the development of psychotic disorders (Keller and Miller, 2006; Wang *et al*., 2005), these cumulative approaches have proven largely inconclusive. Thus, major individual genes with small or moderate effects (examined via early linkage and candidate association studies) are unlikely to be responsible for susceptibility to – or the onset of – psychosis. Rather, schizophrenia spectrum disorders – or SSDs – are probably far more likely accounted for by a *polygenic* model, whereby some gene variants (including in combination) and more recently explored rare point mutations (e.g., copy-number variants, or CNVs) contribute small effects, as well as other genetic (e.g., epigenetic) factors (see Gebicke-Haerter, 2012). A number of reviews have explored some of the major individual candidate genes initially believed to contribute to a polygenic model of SSDs and more recent evidence pointing to genetic factors beyond GWAS and CNVs (Rodriguez-Murillo *et al*., 2012; for a brief overview see Walder, Ospina *et al*., 2012). In this section, we summarize this line of research and point to additional more recent findings examining DNA methylation and histone modifications.

The earliest genetic studies aimed at identifying genes underlying psychosis included linkage studies, which assess the tendency of certain loci to be inherited together. These studies demonstrated inconsistent results, though a recent meta-analysis of 32 linkage studies revealed a number of significant linkages, particularly on chromosomes 2q and 5q (Ng *et al*., 2009). Other approaches such as positional candidate genes studies, which prioritize genes in known linkage regions, have been more successful in discovering promising susceptibility genes (Ross *et al*., 2006). These genes include *dysbindin* (*DTNBP1*), *D amino acid oxidase activator* (*DAOA*), *DISC1*, and *neuregulin 1* (*NRG1*). *DTNBP1* was first identified as a gene associated with schizophrenia through linkage on the chromosome 6p (Straub *et al*., 2002) and is thought to influence glutamate neurotransmission (Numakawa *et al*., 2004). Chromosome 13, which includes the *DAOA* gene, has strong linkage regions to schizophrenia (Detera-Wadleigh and McMahon, 2006); *DAOA* activates D amino acid oxidase, which is a coagonist at NMDA glutamate receptors. *DISC1*, found on chromosome 1, has been implicated in schizophrenia, bipolar disorder, and other major mental illnesses (Hennah *et al*., 2006). Although its molecular mechanism is unknown, *DISC1* is thought to be involved in brain development and adult neuronal functioning such as neuronal migration and maturation, synaptic transmission and plasticity. *NRG1* was identified as a candidate gene via fine-mapping of a locus on chromosome 8 (Harrison and Law, 2006) and has been subsequently

linked with schizophrenia. Finally, *NRG1* encodes many types of mRNA and proteins that influence cell signalling, axon guidance, synaptogenesis, glial differentiation, myelination, and neurotransmission (Corfas *et al.*, 2004). The mechanisms by which altered *NRG1* function might lead to schizophrenia remain unclear, however.

More recently, the creation of the entire human genome-wide map of 3.1 million single nucleotide polymorphisms (SNPs) has allowed researchers to conduct GWAS (Frazer *et al.*, 2007). GWAS have the ability to detect small effect genes while not requiring the knowledge of specific pathogenesis. One such study based on pooled DNA sampling reported a significant association to the *REELIN* gene, believed to encode a protein involved in neuronal positioning and neuronal development (Shifman *et al.*, 2008). GWAS based on individual genotyping have implicated genes such as *colony stimulating factor 2 receptor alpha* (*CSF2RA*), which is thought to regulate granulocytes and macrophages, and *short stature homeobox isoform b* (*SHOX*), which is a transcription factor whose involvement is still unknown (Lencz *et al.*, 2007). Interestingly, another GWAS based on individual genotyping for schizophrenia revealed a significant result for the *zinc finger protein 804A* gene (*ZNF804A*) only when the phenotype was expanded to include bipolar disorder (O'Donovan *et al.*, 2008). Therefore, *ZNF804A* is very likely a susceptibility locus for both schizophrenia and bipolar disorder, which share similar clinical symptomatology (and which have been associated with creativity; e.g., Eysenck, 1993; Jamison, 1993). Later, we discuss potential shared genetic factors implicated in both psychosis and creativity.

GWAS technology also allows for the assessment of CNVs, which are stretches of genomic deletions and duplications ranging from 1 Kb to several Mb that can vary between individuals. One of the most consistent findings using CNV analysis is the role of chromosome 22q11; a deletion of chromosome 22q11 increases the risk for schizophrenia approximately 25-fold (Murphy *et al.*, 1999). With regards to individual CNVs implicating specific genes, Kirov *et al.* (2008) identified a rare deletion affecting part of gene *NRXN1*, which has been previously implicated in autism and mental retardation (Szatmari *et al.*, 2007). They also observed a *de novo* duplication of *amyloid beta A4 precursor protein-binding* (*APBA2*), a protein that interacts with *NRXN1*. Together, *NRXN1* and *APBA2* are believed to play a role in synaptic development and function.

Most recent GWAS studies have failed, however, to demonstrate convergence of findings across investigations. Environmental effects also contribute to the etiology of psychotic disorders through epigenetic means. Epigenetics is the study of heritable – but reversible – changes in gene expression that occur without any changes in the genomic DNA sequence

such as DNA methylation (Pidsley and Mill, 2011). Growing evidence for DNA methylation in schizophrenia mainly involves candidate genes associated with neurotransmitter function such as *REELIN* (Abdolmaleky *et al.*, 2004). Altered function of serotonin has also been implicated in the increased susceptibility of a number of psychiatric disorders, including schizophrenia (Gaddum and Hameed, 1954). Methylation of a serotonin-related allele (*HTR2A* C102) has been found to correlate with DNMT1 expression levels (Polesskaya *et al.*, 2006). DNA methylation analyses of *COMT* (believed to play a role in schizophrenia) have discovered respective reductions in the promoter in approximately 50 percent of patients (Abdolmaleky *et al.*, 2006). These results demonstrate that DNA methylation provides a viable option for better understanding the development of psychotic disorders.

In sum, despite the complexity of polygenic models of gene expression, in which a large number of genes contribute small to moderate effects for developing a disorder, and the fact that the study of the genetic basis of psychosis and other mental disorders is in its infancy, researchers have identified a fair number of genes that appear to be associated with SSDs. However, their complex inter-relationships and roles remain ambiguous.

Genes associated with creative thought

The methodological and conceptual complications inherent in the study of the genetic basis of psychosis are echoed and perhaps even intensified in the study of the genetic basis of creative thought. Creativity itself has only been the subject of scientific investigation in the last 60 years or so (see Guilford, 1950), with a notable acceleration in the past two decades. There is broad agreement that creativity involves the ability to generate novel and useful ideas and behaviors, which are then implemented in everyday life. However, assessments of novelty and value occur against the backdrop of sociocultural factors (Csikszentmihalyi, 1988; Sawyer, 2006), which can be construed as largely subjective. Indeed, the whole enterprise of understanding creativity from neurological or genetic perspectives is rife with controversy. For instance, as Gardner (2001) argued, "You could know every bit of neurocircuitry in somebody's head, and you still would not know whether or not that person was creative" (p. 130). Sawyer (2006) bluntly stated, "We can't look to genetics for the explanation of creativity" (p. 94).

However, the notion that there is a heritable aspect of at least some aspects of high ability (including creativity) is a venerable one, going back at least to Francis Galton's book *Hereditary genius* (1869). Earlier studies of monozygotic versus dizygotic twins, which provide an estimate of

genetic heritability, yielded somewhat mixed results. For instance, Barron (1972) found evidence for heritability of aspects of creative thought like adaptive flexibility and aesthetic judgment of visual displays, but no evidence of heritability for the ability to generate numerous ideas or original ideas; Vandenberg (1968) and Reznikoff *et al.* (1973) found no evidence for the heritability of divergent thinking or other putative aspects of creative thought. However, more recent research by Vinkhuyzen *et al.* (2009) looking at both normal and high levels of ability in diverse (and plausibly creative) domains like music, art, writing, language, chess, mathematics, sports, as well as in memory and knowledge, have revealed high heritability rates – ranging from .32 to .71 for aptitude measures and .50 to .92 for talent measures in these domains. Thus, the extent to which aspects of creativity, or at least creative potential, has some genetic basis remains at the very least an open question, with recent results suggesting a relatively strong association.

If this is the case, then what are the genetic variations associated with cognition, personality, and behavior that bestow on an individual more creative capacity than the average person and, thus, perhaps render him or her more reproductively successful? This is not a question with a simple answer. Analogous to the polygenic view that multiple genes jointly confer a probabilistic risk for developing complex mental illnesses on the individual (Hyman, 2000), recent studies in creativity research similarly demonstrate the existence of several genes that appear to contribute to individuals' creative abilities (Reuter *et al.*, 2005). This is understandable given that it is highly likely that creative behaviors involve a widely distributed network of brain regions (Chávez-Eakle, 2007), and also that genes and complex behaviors (such as creativity) are unlikely to have direct, simple links with these regions (Kandel, 1998).

This polygenic perspective on creativity is indispensable in our discussion of genetic bases of creativity, because creativity is not a unitary or homogenous entity but rather involves a conglomeration of cognitive components (Amabile, 1996; Sternberg and Lubart, 1995). Among the more prominent components are: ideational or cognitive *fluency*, in which (many) raw ideas are generated or conceptually combined; the ability to devise *original* or novel ideas, typically defined in terms of their statistical infrequency; cognitive *flexibility*, or facility in switching attentional focus from one domain to another (Guilford, 1967; Torrance, 1969); the ability to *discern* promising ideas from those that are unlikely to lead to creative final outcomes (Silvia, 2008). This is by no means an exhaustive list; moreover, such processes are unlikely to be exclusively associated with creative cognition. The multiplicity inherent in creative thought is also evident when considering that creative achievement across various

domains often draws on different sets of cognitive abilities and behavioral skills (Kaufman and Baer, 2005).

Despite the daunting variability in the cognitive and behavioral components that constitute creative abilities, some research has begun to investigate the genetic basis of creativity. In particular, dopamine (DA) receptor genes, which are related to the brain's dopaminergic functioning, have been targeted. Notably, dopamine receptor genes are simultaneously relevant to psychopathology and creativity, because several studies have pointed to the importance of intact dopaminergic signaling for normal and efficient prefrontal functioning necessary for working memory (Sawaguchi and Goldman-Rakic, 1991) and attention (Nieoullon, 2002). Additionally, there is some evidence to suggest that personality traits associated with creative behavior are affected by dopaminergic signaling (Reuter *et al.*, 2005). In particular, a tendency for novelty seeking has been generally found to be associated with D4 receptor gene (DRD4) polymorphisms (Epstein *et al.*, 1996). Such research findings have sparked interest in trying to find a link between dopamine-related genes and creative thought processes. One positron emission tomography (PET) imaging study found a negative correlation between divergent-thinking abilities and D2 receptor densities in the thalamus region (de Manzano *et al.*, 2010), further supporting the idea that dopamine availability has important influence on creative thought processes.

Interestingly, in schizophrenia, abnormal dopaminergic functioning in the thalamic region has been previously associated with psychotic symptoms and genetic risks of psychosis (Bucksbaum *et al.*, 2006; Talvik *et al.*, 2003). A specific allele (A1+) of the D2 receptor gene (*DRD2*) has also been linked with verbal creativity, whereas the A allele of the *TPH1* gene was associated with figural and numerical creativity (Reuter *et al.*, 2006). In regards to a more behavioral manifestation of creativity, *AVPR1a* and *SLC6A4* gene polymorphisms were found to be associated with creative dance performance (Bachner-Melman *et al.*, 2005).

In the same family of dopamine-related genes, there has been some demonstration of a link between dopamine (DA) transporter genetic polymorphisms and an important component of creative thinking ability – namely, attentional cognitive flexibility. Studies have shown that individuals homozygous for the 9-repeat allele of the *DAT1* dopamine transporter gene have a greater advantage over those without a 9-repeat allele in one's ability to detect task novelty (Garcia-Garcia *et al.*, 2010) and also greater cognitive readiness to be attentionally flexible (Colzato *et al.*, 2010). Presumably such a difference is accounted for by the variability in *DAT1* polymorphism that affects individuals' striatal DA availability. This association influences individuals' adeptness at changing their focus of

attention, which may in turn mediate a creative thinking process of rapidly shifting attentional focus and making original connections between unrelated objects or items. Interestingly, one study (White and Shah, 2006) has shown that adults diagnosed with attention-deficit/hyperactivity disorder (ADHD) could generate more items in a divergent-thinking task (i.e., an unusual uses task, in which participants are asked to think of many possible alternative uses of a common object), demonstrating a cognitive advantage in terms of ideational fluency (although it should be noted that ADHD-diagnosed participants also showed compromised convergent thinking and inhibitory control in other tasks).

Due to its functional significance in dopaminergic functioning, the Catechol-O-Methyl-Transferase (*COMT*) gene and its polymorphisms have also been a focus of active research in the past decade. While the general body of behavioral genetics literature points to the finding that reduced *COMT* activity related-genotypes (i.e., Val158Met polymorphism) are associated with higher general intelligence measures (Goldman *et al.*, 2009), studies more specifically investigating their link to creativity have found no association between *COMT* genotypes and measures of creativity (Lu and Shi, 2010; Reuter *et al.*, 2006).

While the aforementioned genes relevant to dopaminergic functioning have undoubtedly been in the spotlight of behavioral genetics research in creativity, other non-DA-related genes associated with cognitive functioning have also received interest in their potential linkage to creative thinking and behavior. In one study, 5-HTTLPR polymorphism of the serotonin (5-HTT) transporter gene was associated with verbal and figural creativity, in that participants who had short/short (s/s) alleles and short/long (s/l) alleles showed greater verbal creativity than those with long/long (l/l) alleles of the genetic polymorphism (Volf *et al.*, 2009). The same study additionally reported that the s/s type had greater figural creativity compared with both the s/l and s/s types. Interestingly, individuals with the short allele of the 5-HTTLPR polymorphisms are also considered to have lower transcriptional efficiency in the promotor region of the serotonin gene compared with those with the long allele of the polymorphism (Lesch *et al.*, 1996), and this seems to confer on them disproportionate risk toward developing depression under stressful life experience (Caspi *et al.*, 2003) – although recent evidence (Pluess *et al.*, 2010) on the "differential sensitivity" hypothesis suggests that, with positive developmental experiences, such individuals are also more likely to experience positive outcomes (e.g., reduced neuroticism). Adding to this indirect evidence of link between serotonergic functioning and creativity is that some psychiatric patients who receive selective serotonin reuptake inhibitor (SSRI) treatment complain of emotional blunting (Opbroek

et al., 2002) and diminished creativity (Bolling and Kohlenberg, 2004)
associated with the intake of SSRI medication. Research on the cogni-
tive and behavioral relevance of serotonergic functioning in relations to
creativity is still scarce, and further research will be needed to clarify the
connection between them.

In sum, despite ongoing controversy about the relevance of genetics
to understanding the phenomenon of creativity, there appears to be at
least some direct preliminary evidence linking aspects of creative thought
to specific genes. Moreover, these genes appear to be related to brain
systems often invoked in discussions of creativity – as well as some types
of psychopathology. In the next two sections, we make explicit some
alleged linkages between mental illness and creativity, both in terms of
cognitive and personality factors, and at the genetic level.

General links between mental illness and creativity

As suggested by the Aristotle quotation that serves as this chapter's epi-
graph, there is a long anecdotal history of associating mental illness and
creativity. Indeed, in this chapter, our argument thus far has implicitly
assumed that there exists some kind of connection between at least some
aspects of mental illness (specifically, psychosis) and some aspects of cre-
ativity. But to what extent does this alleged association withstand rigorous
scientific scrutiny? Researchers and scholars interested in this issue have
implemented a variety of methodologies in pursuing it. These include
anecdotal and biographical case studies of creative persons – either indi-
vidually or as part of larger samples – as well as measures of intelligence
and personality, laboratory tests of other cognitive constructs, and func-
tional neuroimaging. Given the complexity and multidimensionality of
mental illness and creativity, in order to obtain reliable information about
the association between the two, it is necessary to narrow the scope of
investigation to very particular aspects of each construct (Silvia and Kauf-
man, 2011), regardless of the method used. Since this level of clarifica-
tion is rarely achieved, a key point in this section is that definitive answers
about the association between mental illness and creativity are still rather
elusive. However, on our particular topic of the relation between gen-
eral creative thought processes and the thought processes associated with
schizotypy, the available empirical research suggests some likely patterns
of association.

In this section, we first briefly review some more general lines of evi-
dence on the association between mental illness and creativity. Case
studies represent perhaps the most venerable line of research in this vein.
Biographical accounts of eminent creative historical figures often describe

the presence of mental disorders such as mood disorders (major depression and bipolar spectrum disorders) as well as episodes of psychosis and other SSDs. Among the many famous cases of alleged mood disorders are Vincent van Gogh, Martin Luther, Ernest Hemingway, Winston Churchill, and Theodore Roosevelt (see Andreasen, 2008). Others are known for also having family members with mental illness (bolstering the case for a genetic link), such as James Joyce, whose daughter had schizophrenia and schizotypal traits; Albert Einstein, whose son had schizophrenia with schizotypal and eccentric traits; and Bertrand Russell, who had many relatives with schizophrenia/psychosis (Andreasen, 2011). However, as Silvia and Kaufman (2011) noted, such case studies suffer from a number of intrinsic limitations, including generalizability across creators as well as judges. That is, many case study reports involve a single judge (usually the author of the case study), who had specific reasons for picking the subject, thereby focusing on the traits and life experiences of the creator that support their conclusion. Therefore, in many case studies, participant and judge are confounded.

Indeed, rigorous research designed to examine the association of creativity with mental illness is laced with multiple challenges, such as identifying the optimal sample and comparison group, as well as defining the nature of the sample and even defining the terms "creativity" and "mental illness" (Andreasen, 2008). In an effort to empirically test the creativity–psychosis hypothesis, some researchers have studied more global patterns by examining larger samples of creative individuals. Several empirical investigations have been conducted on historically important creative individuals. For example, Ludwig (1995) reviewed information on 1,004 individuals considered to be influential in the twentieth century and reported high rates of alcoholism, schizophrenia, and mood disorders. Andreasen's (1987) study of currently living highly creative individuals, conducted at the University of Iowa during the 1970s and 1980s, was rooted in empirical evidence of famous cases coupled with a theoretical underpinning based on the possibility that the frequently observed cognitive trait among individuals with psychosis – namely, a capacity to see the world in a novel and original way – may be shared by creative people who likewise can see things that others cannot (Andreasen, 2011). Andreasen's study did not reveal a link between creativity and psychosis, although she did report an elevated level of mood disorders among creative writers. Others (Jamison, 1993; Ludwig, 1995) have reported concordant results using personal interviews of participants towards determining diagnosis using modern conceptualizations of depression and bipolar disorder. Along similar lines, Post (1996) studied 291 British and American creative achievers and reported

similarly high incidences of mood and SSDs in participants and their family members.[1]

This research led to the second Iowa study of creative genius, still ongoing, which uses a case-control comparison design (Andreasen, 2011). This neuroimaging study attempts to compare highly creative individuals, defined as those who have won a major award in their field (e.g., Nobel or Pulitzer prizes), with "non-creative" controls on measures of intelligence and personality as well as functional neuroimaging. The latter uses a paradigm that activates the association cortices, those most active when engaged in free-ranging and uncensored thought. Preliminary findings have revealed that brain activations in these areas are stronger among creative individuals, and comparable between artists and scientists. However, limited sample size to date precludes conclusions about creativity differences as a function of mental illness.

In sum, while such studies are interesting and suggestive, the precise nature of the association between creativity and mental illness remains difficult to delineate, and as yet there is no general-purpose answer (Silvia and Kaufman, 2011). There are different levels of creative achievement (e.g., little-c versus Big-C: Kaufman and Beghetto, 2009), different aspects of creative cognition (e.g., conceptual combination, divergent thinking, latent inhibition), and different degrees and kinds of illness expression (e.g., schizophrenia, positive schizotypy, negative schizotypy), which do not necessarily map onto each other in a uniform manner. For instance, while schizophrenia tends to be marked by debilitating symptoms across positive, negative, and disorganized symptom domains, artists who demonstrate schizotypal traits tend to experience positive symptoms (e.g., unusual perceptual experiences, magical beliefs) more so than negative or disorganized trait dimensions (Nelson and Rawlings, 2010), while mathematical and scientific creativity tends to be associated with negative schizotypal traits (e.g., physical and social anhedonia, introversion) (Nettle, 2006; Rawlings and Locarnini, 2008). As Silvia and Kaufman highlight, researchers attempting to investigate the nature of the relation between mental illness and creativity need to specify the various levels of creative achievement, aspects of creative cognition, and illness expression under investigation.

Because, in this chapter, our focus is primarily on general creative thought processes and the thought processes associated with schizotypy (characterized by eccentricity, magical thinking, and unusual

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[1] Importantly, however, see Schlesinger's (2009) strong methodological critique of this whole line of inquiry, which in her view casts considerable doubt on the strength of the popular 'genius-madness' association.

experiences), we now focus on research investigating links between these constructs. In recent years, a number of theorists and empirical studies have explored possible linkages between creative cognition and schizotypy, with some suggestive findings. For example, Eysenck (1993) argued that certain aspects of cognition associated with high scores on a psychotic personality dimension (e.g., overinclusive thinking) might facilitate originality and, under optimal circumstances, creative thinking. One study examining 100 students found a significant correlation between intensity of psychoticism and creativity, as measured using divergent-thinking tasks (Woody and Claridge, 1977). O'Reilly *et al.* (2001) reported that creative art students scored higher on creativity measures as well as on the unusual experiences dimension of schizotypy compared with students in the humanities. Burch *et al.* (2006) also demonstrated higher rates of schizotypy in a sample of visual arts students compared with students in other academic departments. A more recent study (Nelson and Rawlings, 2010) found interesting linkages between the positive symptoms of schizotypy and normally varying personality traits: in a sample of 100 artists, positive schizotypal traits were the strongest predictors of aspects of the creative experience, including absorption and power/pleasure. Further research suggests that absorption is aligned with the personality trait Openness to Experience distinctly from Intellect. For instance, DeYoung *et al.* (2011) found that the Openness/Intellect domain of personality comprised a simplex of traits, with Openness at one end and Intellect at the other. Absorption was one of the best markers of Openness, while a traditional measure of intelligence was one of the best markers of Intellect.

What cognitive mechanisms underlie schizotypy? DeYoung *et al.* (2011) argued that positive schizotypy is in large part due to the false detection of patterns through an overfiring of causal connections, known as apophenia. Accordingly, positive schizotypy involves an overactive implicit learning system. In support of this, recent research has found a correlation between Openness to Experience and implicit learning ability (Kaufman *et al.*, 2010). In the latter study, implicit learning was not related to Intellect, further suggesting that the cognitive mechanisms that underlie positive schizotypy specifically also underlie Openness to Experience.

Another plausible cognitive mechanism associated with both schizotypy and creative cognition is the construct of latent inhibition. Latent inhibition is a gating mechanism that screens from conscious awareness information previously tagged as irrelevant. Carson *et al.* (2003) found that reduced latent inhibition was associated with creative achievement among a high-IQ sample. They proposed that decreased latent inhibition

increases creativity by allowing irrelevant stimuli to enter one's conscious awareness, thereby increasing the number of novel and useful combinations of stimuli.

Taken together, these studies suggest that: (1) creative persons (particularly artists) have higher levels of positive schizotypy and a propensity for psychosis, and (2) milder symptoms are more conducive to creativity than more severe forms of SSDs. With these preliminary associations in mind, we next look at common genetic linkages between these creative mental processes and schizotypy.

Genetic links between creativity and schizophrenia spectrum disorders

Despite the provocative links between psychosis and creativity outlined in the previous sections of this chapter, and the apparent heritability of both constructs, few empirical studies have been conducted to directly assess or identify genes that potentially undergird both psychosis and creativity. While such research is in its earliest stages, several notable findings have emerged.

For instance, Kéri (2009) argued that the neuroregulin 1 gene (*NRG1*) is linked to both increased risk for psychosis (see Mei and Xiong, 2008) and creative achievement, particularly in individuals with high intellectual and academic achievement (see also Venkatasubramanian and Kalmady, 2010). Kéri focused on a particular polymorphism of *NRG1,* SNP8NRG243177/rs6994992 (C versus T), where the T/T phenotype is associated with an increased risk for psychosis and lower premorbid IQ (Hall *et al.*, 2006), lower working memory capacity (Stefanis *et al.*, 2007), and neurodevelopment and synaptic plasticity (Harrison and Law, 2006). Participants were administered measures of schizotypy and creativity, and genomic DNA was extracted. Kéri discovered that individuals with the T/T phenotype demonstrated significantly higher divergent-thinking scores (e.g., originality, flexibility, and fluency) compared with the other phenotypes. While no direct link was made between creativity and a risk for developing psychosis in the study sample, this line of research suggests that *NRG1* may be simultaneously related to psychopathology and creativity. This is one of the first studies suggesting that a genetic polymorphism linked to mental illness may confer an advantage in psychological functioning by means of higher creative, intellectual functioning.

A common area of interest with regards to overlap among mental illnesses and creativity concern genes that code for neurotransmitters and neurotransmission. For example, dopamine (D2) receptor sensitivity, a

neurotransmitter highly associated with psychosis, has been linked with decreased latent inhibition (Wang *et al.*, 2004), that is, the inability to filter extraneous and potentially distracting information from the environment, an individual-difference variable that has been linked to creativity (Carson *et al.*, 2003; Carson, this volume). As mentioned previously, the gene *COMT*, which is involved in the regulation of dopamine levels, has also been implicated in psychotic disorders and as contributing to various cognitive processes. For instance, the Val allele of the Vall58Met polymorphism allows for greater expression of *COMT* (and therefore lower levels of dopamine) in the prefrontal areas (Honea *et al.*, 2009). While the Val+ allele has been linked with SSDs (Egan *et al.*, 2001), the Val− allele has been associated with higher IQ, working memory, and cognitive flexibility, a common characteristic of creative behavior (Joober *et al.*, 2002; Malhotra *et al.*, 2002). There is also recent evidence of *COMT* modulation of neuroendocrine (hypothalamic-pituitary-adrenal) activity (e.g., cortisol) among adolescents at risk for psychiatric disorders, including psychosis (Walder *et al.*, 2010).

As in psychotic disorders, serotonin has also been implicated in creative ability, as discussed earlier. The gene *SLC6A4* (also called *5HTT*), which is thought to regulate synaptic levels of serotonin, has been associated with personality constructs of creativity, such as increased scores on assessments of Openness to new experiences (Stoltenberg *et al.*, 2002). More recently, the short *SLA6A4* promoter region polymorphism has been associated with creative dancing ability, such that altered serotonin levels are theorized to increase ability for imagery and attention to stimuli (Bachner-Melman *et al.*, 2005). Along similar lines, Volf *et al.* (2009) found that individuals with the short allele of the 5-HTTPR polymorphism of the *5HTT* gene demonstrated significantly higher levels of verbal creative ability than individuals with an l/l configuration, and individuals with an s/s genotype demonstrated higher figural creativity scores compared with carriers of the L allele. Other evidence for the influence of serotonin levels on creativity includes the *A779C* polymorphism of the *TPH1* gene, which influences the enzyme that regulates levels of 5-HT, which has been linked to schizophrenia and suicide (Abbar *et al.*, 2001; Zaboli *et al.*, 2006). Reuter *et al.* (2006) discovered that carriers of the A allele of *A779C* polymorphism scored higher on measures of figural and mathematical creativity compared with carriers of the C allele in a group of university students.

Further creativity research focusing on specific positional candidate genes has revealed a genetic influence of *AVPR* polymorphism. Again, Bachner-Melman *et al.* (2005) revealed an association with the *SLC6A4* polymorphism and creative dance; however, they also discovered an

association with creative dance and the *AVPR1a* polymorphism. The AVP (or arginine vasopressin) receptor 1A is coded by the *AVPR* receptor 1A gene and has been observed to influence the AVP hormone in the brain, which is thought to affect social, emotional, and behavioral traits such as aggression (Thompson *et al.*, 2004), parenting (Hammock and Young, 2006), and love (Zeki, 2007). Also, Ukkola *et al.* (2009) assessed the genetic influences on musical creativity and discovered a significant relationship with musical ability and the haplotype RS1 + RS 3 of the *AVPR1A* polymorphism. Finally, Reuter *et al.* (2006) ambitiously set forth to discover the first candidate genes for creativity, focusing particularly on polymorphisms of *COMT*, *DRD2* and *TPH1* genes, because they have been implicated in executive cognitive functioning. They discovered no relationship between *COMT* and creativity measures, while the *DRD2* TAQ 1A allele was associated with verbal creativity and the *TPH1* A779 allele was associated with figural creativity.

In sum, despite limited direct support, there is converging evidence of some shared genetic underpinnings of psychosis and creativity. This result is in line with long-standing anecdotal speculation about the relation between mental illness and creativity, as well as more recent cognitive research identifying loose, flexible mental processes that play out in similar (if not identical) ways in schizotypal and creative thought.

Limits of these explanations

The conceptualization in the preceding sections is clearly preliminary, relying on early genetic studies of creativity and SSDs that have been conducted only in recent decades, and is thus presented with caution. Surely, future research techniques elucidating these issues will increase in sophistication, scope, and detail. Nevertheless, it is impressive how much progress has been made so far, both at the levels of theories and specific empirical results in producing a coherent genetic perspective linking aspects of psychosis and creativity. Thus far, the key elements in this perspective have focused on the activity (including interaction) of several genetic factors (in the context of environmental influences), including genes that code for neurotransmitters like dopamine and serotonin. If we imagine the likely improvements in technology and measurement that will be applied to this question in the coming years and decades, it may be useful to consider some of the potential limitations of this approach.

On the theory side, our current understanding of all of the issues raised in this chapter is limited by the way in which the relevant constructs have been conceptualized up to the present time. This point applies to the action of genes and possible mechanisms relating genes to cognitive

processes and behaviors, general evolutionary models (including sexual
selection models) explaining the evolutionary persistence of seemingly
disadvantageous traits, as well as mental illnesses and our understanding
of the nature of human creativity. Indeed, as detailed by Miller (2010),
evolutionary genetics is an emerging field that is in flux, as is our under-
standing of the genetic factors contributing to mental illnesses and cre-
ative ability. Thus, theoretical considerations must continue to evolve in
tandem with new knowledge gained in the field. As each of these bod-
ies of theoretical work evolves and is constrained by emerging empirical
findings (and the associated technological advances allowing such find-
ings), we might expect some aspects of our basic understanding of these
issues to change, maybe quite radically.

Similar issues pertain to the scientific study of creativity. As noted
by Silvia and Kaufman (2011), many basic questions about the relation
between mental illness and creativity simply remain unanswered, largely
because the questions have not been asked with sufficient specificity
or addressed with sufficient methodological rigor. Thinking even more
broadly, it is probably fair to state that many issues about the fundamental
nature of creativity remain poorly understood; these lacunae have almost
certainly colored our understanding of how creativity may be related
to psychosis and other mental illnesses. For instance, throughout this
chapter, we have characterized the loose, disorganized thought patterns
evident in schizotypal thinking as being closely associated with mental
processes like divergent thinking and distant conceptual combinations
that are traditionally regarded as essential to creativity.

However, such idea-generating cognitive processes typically represent
only the very beginning of the creative process. Many sophisticated mod-
els of creativity (e.g., Martindale, 1990; Simonton, 1984; Ward *et al.*,
1999) posit two fundamental regimes of creative thought: a largely
unconscious process of generating ideas, followed by a largely conscious,
goal-directed process of elaborating them into finished creative products.
Currently, such models typically show a peculiar bias whereby generat-
ing ideas is given priority as *the* essential engine of creativity, while idea
elaboration is often underemphasized and undervalued (Kozbelt, 2009).
However, mounting evidence (e.g., Fayena-Tawil *et al.*, 2011; Kozbelt,
2006, 2007, 2008; Silvia, 2008) suggests that the kinds of evaluative and
goal-directed cognitive processes typical of idea elaboration play a far
more important role in creative productivity than has been traditionally
recognized.

Elaborative processes are certainly critical for the creation of com-
plex, domain-specific Big-C creative achievements, such as symphonies
and novels – a process virtually always rife with revision and rethinking.
The main links between psychosis and creativity, however, have almost

exclusively emphasized idea generation rather than idea elaboration (Kozbelt, 2009). Reconceptualizing the general nature of creativity to give greater weight to elaborative processes has the potential to shift the balance away from the potential psychosis–creativity association, at least for instances of very high levels of creative achievement. The extent to which any genetic basis might be identified for such complex cognitive and socioculturally informed processes is difficult to assess, particularly because, as with evolutionary genetic models of schizophrenia, such an alternative framework of creativity has yet to be worked out in detail.

Despite potential limitations towards understanding these complex issues, the nature and origins of a possible association of creativity with psychosis may slowly become clearer as the field gains an increasingly sophisticated understanding of the complexity of polygenic influences on the mind, brain, and behavior – including the importance of gene sequencing and the role of epigenetics (including environmental influences). Importantly, rather than vying for a singular explanation, a healthier and sounder approach likely will be more integrative. From an evolutionary perspective, an optimistic appraisal of the outcome of this line of research would be something like a multilevel synthesis of theoretical approaches that integrates, as one possible explanation, sexual selection with evolutionary genetics. Potentially, this would move the dynamic of scholarly discussion and debate away from the current surfeit of (albeit non-mutually exclusive) models described early in the chapter toward a more integrated and parsimonious position. Such a model would need to account for several key findings (among others): (1) the evolutionary persistence of psychosis in the population worldwide; (2) tentative (although not consistent nor conclusive) evidence of possibly higher likelihood of psychiatric disorders (including across the schizophrenia spectrum) among highly creative individuals; (3) and a link between creative professions and first-degree relatives of schizophrenia patients (see Kyaga *et al.*, 2013); and (4) the modest (albeit not uniform) evidence of an association of creativity with psychotic-like experiences (in the non-clinical range) in the general population (see Kyaga *et al.*, 2013) . Providing a sound, integrative genetic, and environmentally informed, explanation for the evolutionary enigma of the persistence of schizophrenia, and the nature of its relation to creativity, is an enormous challenge – but one which, if the past decade of research is any indication, may well be scientifically tractable.

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