The Temperament – Psychopathology Link: How Does Difficult Temperament Affect Risk for and Presentation of Major Depression Among Offspring at High and Low Risk for Depression

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ABSTRACT

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The current study examined the relationships between parental depression, offspring depression, and offspring temperament among 203 offspring at high or low-risk for depression. Offspring were followed over a 20-year study period. Two primary study aims were addressed. First, we sought to confirm that parental depression predicts offspring lifetime depression and offspring difficult temperament, and that offspring difficult temperament predicts offspring major depression, while adjusting for family effect. Second, we sought to examine the *pathoplasty model* of the relationship between temperament and psychopathology by examining how offspring difficult temperament affects qualitative features of major depression – specifically, frequency, severity, and duration. Results indicate that high-risk offspring have more difficult temperament and are four times more likely to have lifetime major depressive disorder (MDD) than low-risk offspring. In addition, offspring with a difficult temperament are twice as likely to have lifetime MDD than low-risk offspring. Results from aim 2 revealed that difficult temperament predicts greater frequency of lifetime MDEs, but not severity or duration. Finally, individual dimensions of temperament were uniquely associated with frequency, severity, and duration of major depressive episodes differentially across risk groups. Implications and future research directions are discussed.

Keywords: temperament; depression; pathoplasty; high-risk; psychopathology

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Since the four humors of Hippocratic medicine and the writings of the Roman Physician Galen individual differences in human behavior have been an area of great debate. Building upon Hippocrates's notion of the four humors or bodily fluids, Galen proposed four classical temperaments which corresponded to having a predominance of one of the four humors. Individual differences in personality were attributed to an imbalance of the four humors and optimal health was achieved when balance was restored. The melancholic individual was thought to have an excess of black bile and had a generally depressive and pessimistic disposition; the choleric individual had an excess of yellow bile displaying irascibility and irritability; the sanguine individual had an excess of blood which meant a largely optimistic disposition; and the phlegmatic had an excess of phlegm and was generally apathetic and stolid in nature. The four classical temperaments broadly correspond to contemporary classifications and the notion of an imbalance in bodily fluids is now akin to an imbalance in neurotransmitters or other neurological dysfunction. The 20th century has also seen tremendous growth in defining and categorizing psychopathology; however, only recently has the study of temperament become an integral part of the developmental psychopathology literature (Nigg 2006; Rettew & McKee, 2005). The integration of the historical debate on individual differences with present-day taxonomies of psychopathology is increasingly important as we begin to delineate developmental profiles of normal and abnormal development.

Definitions of Temperament

In their seminal New York Longitudinal Study of temperament Alexander Thomas and Stella Chess followed 141 children from 85 upper-middle class families over six years. Thomas and Chess (1977) described temperament as "the way in which an individual behaves" (p. 9) and suggested that temperament was the "how" of human behavior rather than the "what" and "why." Thomas and Chess believed that temperament "must at all times be differentiated from motivation, abilities, and personality" (Goldsmith et al., 1987) which more aptly correspond to the "what" and "why" aspects of human behavior. They believed that the "what" and "why" aspects of behavior developed through interaction with the environment, as opposed to temperament, which was considered more constitutionally-based.

Goldsmith and Campos identify temperament as individual differences in the likelihood of experiencing and expressing primary emotions and arousal (Goldsmith et al., 1987). Temperament must be *a)* emotional in nature, *b)* reflect individual differences (i.e., behavioral tendencies), and *c)* represent an emotional expression. They note that temperament does not include cognitive or perceptual factors, and is not transitory in nature.

Rothbart and colleagues have defined temperament as "constitutionally based individual differences in reactivity and self-regulation, in the domains of affect, activity, and attention" (Rothbart & Bates, 2006, p. 100; see Derryberry & Rothbart, 1984; Rothbart & Derryberry, 1981). *Reactivity* refers to emotional, motor, and attentional excitation measured by latency, intensity, and recovery time, while *self-regulation* refers to processes such as approach-withdrawal and effortful control that modulate reactivity (Rothbart, 2007).

While increasing consensus regarding the general stability, early manifestation, and genetic basis of temperament as well as its manifestation as behaviorally observable individual

differences continues to grow (Nigg, 2006; Rettew & McKae, 2005; Rothbart & Bates, 2006), the boundary between temperament and personality remains an area of considerable debate. Although not a primary focus of this study, a brief examination of the temperament-personality debate is warranted.

Temperament and Personality

Contemporary personality research began with Hans Eysenck's post-WWII research which resulted in a model of personality consisting of three primary traits: *Extraversion* (outgoingness, positive affect, excitability), *Neuroticism* (anxiety, depression, negative affect), and *Psychoticism* (sociability, aggression). Emerging from these traits was Eysenck's fundamental theory of personality comprised of two orthogonal dimensions of personality functioning: introversion/extroversion and neuroticism/stability. Eysenck's theory has been applied and revised by various lines of research and remains as the foundation for current temperament-personality research focusing on higher-order traits. Eysenck's original three traits correlate with contemporary theories of personality such that Extraversion has been variably referred to as *positive emotionality, positive affect, surgency, positive temperament,* or *approach*; Neuroticism has been labeled *negative emotionality, negative affect, negative temperament,* or *withdrawal;* and Psychoticism is now understood primarily as *constraint, or effortful control.* Perhaps the most widely accepted adaptation of Eysenck's original model is the Five Factor Model of Personality (FFM) comprised of the dimensions Neuroticism, Extraversion, Openness to experience, Conscientiousness, and Agreeableness (McCrae & Costa, 1987). The FFM broadly corresponds to dimensions of temperament originally put forth by Thomas and Chess (1977) and in recent years has experienced a resurgence of research interest in regards to

dimensional models of psychopathology. Some theorists have examined the distinction between personality and temperament more explicitly.

Several lines of research have emerged. Cloninger's psychobiological theory of personality (Cloninger, Svrakic, & Przybeck, 1993) asserts that personality is comprised of *temperament* and *character* whereas temperament refers to "individual differences in their automatic responses to emotional stimuli, which follow the rules of associative conditioning or procedural learning of habits and skills. Temperament traits include basic emotional response patterns such as fear, anger, and attachment" (p. 2). As the individual matures through the socialization process, they develop character, which refers to "individual differences in our voluntary goals and values, which are based on insight learning of intuitions and concepts about our self, other people, and other objects" (p. 3). Cloninger's theory of personality distinguishes between the biological components driving human behavior and their inevitable interaction with the environment.

Rather than breaking down personality into component parts, Kagan (1997) puts forth a model of development whereby temperament is the foundation for later personality development. Accordingly, temperament is primarily relevant during childhood whereas personality is applicable in the domain of adulthood. Similar to Kagan (1997), Rothbart (2007) asserts, "Temperament describes the initial state from which personality develops and links individual differences in behavior to underlying neural networks. Temperament and experience together 'grow' a personality, which will include the child's developing cognitions about self, others, and the physical and social world, as well as his or her values, attitudes, and coping strategies" (Rothbart, 2007, p. 207). These views differ slightly from Chess and Thomas who view temperament as most directly expressed in early childhood/infancy, but also observable in pure

form in adulthood, particularly when "novel environmental challenges render coping skills ineffective" (Goldsmith, et al., 1987; p. 507).

In sum, scientific definitions of temperament illustrate the recent shift towards a more complex understanding of the biological underpinnings of temperament and how they interact with context, thereby contributing to the development of adult personality. However, this interactive process does not render temperament obsolete in adulthood. As Thomas and Chess suggest, when coping strategies prove ineffective under stress, raw temperament may be activated in its purest form. This concept is particularly relevant when examining the relationship between temperament and psychopathology as major mental disorders are often related to inadequate coping patterns in the face of environmental stressors.

Dimensions of Temperament

Thomas and Chess' (1977) seminal New York Longitudinal Study yielded nine dimensions of temperament: 1) *Activity Level* – motoric activity and proportion of active versus inactive periods; 2) *Approach/withdrawal* – initial response to novel stimuli; 3) *Intensity of Reaction* – irrespective of quality or direction of response; 4) *Threshold of Responsiveness* – necessary stimulation to evoke response to novelty irrespective of quality or direction; 5) *Adaptability* – responses to new or altered situations regardless of initial response; 6) *Rhythmicity (regularity)* – predictability of eating, sleeping, or other physiological functions; 7) *Quality of Mood* – amount of pleasant, joyful behavior versus unpleasant, irritable behavior; 8) *Attention Span/Persistence* – length of time spent on an activity and continuation in face of obstacles; and 9) *Distractibility* – susceptibility to interference from environmental stimuli. From these nine dimensions three temperament profiles emerged. Chess and Thomas (1990) found that roughly two-thirds of the 141 children fit into one of the following three profiles: 1)

"the easy child" – 40 percent – high approach to novelty with positive, engaged mood; 2) "the difficult child" – 10 percent – high activity, high intensity, low rhythmicity, withdrawal from novel stimuli, and high negative mood; 3) "the slow to warm up child" – 15 percent – high reactivity to novelty combined with some negative emotion. The remaining third did not fit nicely into one of these three categories.

Rothbart and colleagues (Derryberry & Rothbart, 1984; Rothbart & Bates, 2006; Rothbart & Derryberry, 1981) approach the construct of temperament from a psychobiological perspective. In their model, temperament is most broadly comprised of individual differences in *reactivity* and *self-regulation*. Reactivity reflects responsiveness to external or internal environment assessed by latency, intensity, and duration of response. Self-regulation refers to a modulation of reactivity by processes such as effortful control and orienting (Rothbart & Bates, 2006). Subsumed under these umbrella terms, Rothbart and colleagues outline two separate, yet overlapping, dimensional models, one applicable during infancy and one during childhood. In infancy, temperament consists of four factors: *negative emotionality*, *surgency/extraversion*, *orienting/regulation*, and *rhythmicity*. As the child develops, negative emotionality and surgency/extraversion remain while orienting/regulation and rhythmicity give way to *high intensity pleasure*, *effortful control/self-regulation*, and *agreeableness/adaptability* (Rothbart & Bates, 2006). This two-part model illustrates the effects of socialization whereby as the child develops he or she is no longer simply orienting and biologically regulating, but is achieving a sense of mastery or control over his or her behavior. The potential for gene x environment interaction is evident in this model.

Neurobiological models of temperament have been proposed as well. Gray's (1991) three-part model of temperament focuses on brain system function, specifically individual

differences in regulating emotion, attention, and activity. Gray described 1) a behavioral activation system (BAS) associated with the caudate and accumbens motor systems, which reflects an individual's sensitivity to rewards; 2) a behavioral inhibition system (BIS) associated with the septohippocampal system, reflecting sensitivity to punishment; and 3) a fight/flight system associated with the amygdala, the hypothalamus, and central gray matter which acts to moderate unconditioned aversive stimuli by mechanisms of defense or escape. Gray (1991) proposed that individual differences in behavior (i.e., temperament) result from variable input and function of these three systems based upon genetic, experiential, or interactive factors.

Cloninger (1986, 1987) also put forth a neurobiological model based on the interconnection of three genetic trait dispositions, each correlated to a specific neurotransmitter system. Cloninger proposed that *novelty-seeking* is associated with low basal activity in the dopaminergic system, *harm avoidance* with high activity in the serotonergic system, and *reward dependence* with low basal noradrenergic activity. In this model, an individual high in novelty-seeking is predisposed to exhilaration and excitement in novel situations leading to the pursuit of rewards, and avoidance of monotony and punishment. Harm avoidance is reflected in strong response to aversive stimuli and subsequent behavioral inhibition of novelty-seeking and acts that elicit punishment. Finally, individuals high in reward dependence tend to respond to signals of reward, including social approval and are resistant to extinguishing previously rewarded behaviors. Cloninger and colleagues (1993) later adapted his theory to include a fourth trait, "persistence," as well as what he termed "character," which included thoughts, beliefs, attitudes, values, coping strategies. Character was hypothesized to develop in adulthood and relate to social effectiveness. Personality, as it were, is fully developed with the integration of temperament and character.

Stability of Temperament

Stability of temperament has generally been assessed using two modes of comparison: rank-order stability and mean-level continuity. *Rank-order stability* – also referred to as the stability coefficient – refers to the maintenance of an individual's position within the group, while *mean-level continuity* refers to normative group-wide changes on any given dimension. For example, Jansen and Mathiesen (2008) found that while certain aspects of temperament underwent significant group-wide change from age 18 months to 9 years (e.g., decrease in activity and sociability) individual rank-order stability remained largely consistent. Here we see the distinction between normative developmental changes in temperament on the group level, as well as the maintenance of positions between individuals over time.

Temperament has been shown to have moderate rank-order stability over time, becoming increasingly stable from early childhood through adolescence. Neppl and colleagues (2010) assessed dimensions of temperament at three developmental phases: toddlerhood (2 year), early-childhood (3-5 years), and middle-childhood (6-10 years). They found that stability coefficients were consistent across these three phases of childhood; yet, the stability coefficient increased successively from toddlerhood to early childhood to middle-childhood, suggesting increasing stability over time. A meta-analysis by Roberts and DelVecchio (2000) found that by early to middle-childhood temperament demonstrates moderate rank-order stability with estimates ranging from .35 to .41.

Other longitudinal studies demonstrate the stability of temperament over time using multiple methods of assessment. Majdandzic and van den Boom (2007) used observational and psychometric questionnaires to assess stability of temperament in four year olds over the course of seven months finding both context-dependent and individual consistency.

Ganiban, Saudino, Ulbricht, Neiderhiser, and Reiss (2008) conducted a study exploring genetic and environmental contributions to temperament from early to late adolescence in a sample of 395 sibling pairs (63 monozygotic twin pairs, 75 dizygotic twin pairs, 58 full sibling pairs, from intact families; and 95 full sibling pairs, 60 half sibling pairs, and 44 unrelated sibling pairs, from stepfamilies). All families were interviewed (each parent completed the EAS – Parent Form; Buss and Plomin, 1984) and observed in their homes at Time 1 (12-13 years) and Time 2 (14-16 years). Using biometric model fitting the authors examined additive genetic, non-additive genetic, shared environment, and non-shared environmental contributions to change or stability of dimensions of temperament. They found stability in most, but not all temperamental traits. Changes in dimensions of emotionality, activity levels, shyness, and sociability, were predicted by both genetic and non-shared environmental factors, while stability of temperament was predicted primarily by genetic factors. In other words, dimensional shifts related to normative development are impacted by nature and nurture, while one's position within the group is impacted primarily by nature.

Few longitudinal studies have explored the stability of temperament beyond adolescence. A study by Windle and Windle (2006), examined stability of temperament from adolescence (*M* age = 15 years) to young adulthood (*M* age = 23 years) and lifetime risk for substance use disorders in a sample of 760 individuals. The authors used the Dimensions of Temperament Scale – Revised (DOTS-R) which assess the following dimensions: General Activity Level, Approach-Withdrawal, Flexibility–Rigidity, Activity Level–Sleep, Positive Mood Quality, Rhythmicity–Daily Habits, Rhythmicity Eating, Rhythmicity Sleeping, Persistence, and Distractibility. The authors found moderate stability from adolescence to adulthood for all dimensions with stability coefficients ranging from .27 to .47. However, they also found

changes in mean level of temperament dimensions over time, specifically, an increase in task orientation (persistence and distractibility) and decrease in general activity and approach.

While very few studies have explored the stability of temperament into adulthood, extensive literature exists on the stability of personality across the lifespan. A particularly comprehensive and rigorous meta-analysis of personality stability was conducted by Ferguson (2010) using more stringent standards for significance of stability and accounting for measurement error, which most studies had not addressed. Using these criteria, Ferguson demonstrated remarkable rank-order stability over the life-span for both general and specific traits, across genders, and for disordered and non-disordered personality profiles. Corrected stability coefficients revealed that personality was least stable in childhood (r = .56) with increasing stability occurring during early adulthood (r = .70), reaching peak stability around age 50 (r = .94), and maintaining this stability into later adulthood (r = .82). This evidence demonstrates that personality, which includes bio-behavioral indices such as response reactivity and regulation components (i.e., temperament), as well as attitudes, values, coping strategies, and defenses exhibits remarkable stability over the lifespan.

In sum, while a final structural model of temperament has yet to be agreed upon, there now exists a general consensus that temperament *a)* manifests early in life, *b)* has a significant genetic basis, and *c)* is moderately stable over time (Nigg 2006; Rettew & McKee, 2005; Rothbart & Bates, 2006; Thomas & Chess, 1977).

Difficult Temperament

Thomas and Chess (1977) first characterized the “difficult child” as one demonstrating high activity, high intensity, and high withdrawal, combined with low adaptability, low rhythmicity, and predominant negative mood. Other temperament researchers, such as Buss and

Plomin (1984) characterized difficult temperament as high emotionality and activity, resulting in a child who becomes easily upset and is difficult to calm down. Rothbart and Derryberry (1981) speak of reactivity and self-regulation rather than difficulty, per se, suggesting prolonged and intense distress reactions as problematic indicators of adjustment. More similar than otherwise, these characterizations all suggest a tendency towards intense emotional and physiological reactivity with poor regulatory capacities.

Difficult temperament has been associated with a wide range of psychological problems across the lifespan including conduct disorders, ADHD, substance abuse, anxiety, and depressive disorders (Bruder-Costello et al., 2007; Chronis-Tuscano et al., 2009; Schwartz, Snidmen, & Kagan, 1999; Watson, Gamez, & Simms, 2005; Windle & Windle, 2006). For example, Guerin, Gottfried, and Thomas (1997) assessed difficult temperament in 104 children at age 1.5 years and obtained parent and teacher-reported behavior problems annually from ages 4-12. Children categorized as having a difficult temperament had greater frequency of attention problems, aggressive behavior, and thought problems. In adolescence and adulthood, difficult temperament has also been linked with poor mental health outcomes. In a 20-year longitudinal study, Bruder-Costello and colleagues (2007) found that difficult temperament in adolescence, characterized by high withdrawal, irritability, and inattention increased risk for lifetime major depressive disorder almost three-fold, and that difficult temperament partially mediated the relationship between parental depression and offspring depression.

Dimensions of difficult temperament have been strongly linked with substance abuse disorders as well. For example, adolescent neurobehavioral disinhibition (Tarter et al., 2003), and low task orientation and flexibility (Windle & Windle, 2006) are associated with development of substance use disorder in early adulthood. In addition, high negative reactivity,

high sociability, and low persistence among 15-16 year-olds predicted later substance abuse (Williams, Sanson, Toumbourou, & Smart, 2000). Williams and colleagues (2000) also demonstrated that offspring at high risk for substance use disorder (SUD) by virtue of parental lifetime diagnosis of SUD were at increased risk for SUD compared to low risk offspring (parents never diagnosed with SUD). Toddlers age 3 who are undercontrolled and inhibited showed higher rates of alcohol problems at age 21 (Caspi, Moffitt, Newman, & Silva, 1996).

A longitudinal study followed 150 children from age 2 to age 5 and examined the differential susceptibility of children with difficult temperament to environmental influences (Mesman et al., 2009). The authors found an overall decrease in externalizing problems over the study period, but also found that children with difficult temperament were more powerfully influenced by sensitive parenting and having more elder siblings than those with an easy temperament. These results support the differential susceptibility hypothesis (Belsky, 1997), which posits that children with difficult temperament are more susceptible to environmental factors whether the outcome measure is positive/adaptive or negative/maladaptive behavior.

The construct of difficult temperament has been associated with a multitude of mental disorders. Research has shown both general and specific effects of certain dimensions of temperament as well as clustering of various dimensions. Yet there exists a relative dearth of evidence examining how difficult temperament affects the presentation of mental disorders, not simply the presence or absence. Given the consensus that temperament emerges early in life, is largely biologically based, and is stable over time, several important questions emerge: What is the nature of the relationship between temperament and mental illness? Beyond predicting increased risk for disorder, how might temperament affect the onset, course, or prognosis of

mental illness? And how might mental illness likewise affect temperament? These scientific inquiries are the focus of the current study and are examined in the following section.

Conceptual Models

The scientific study of the relationship between temperament and psychopathology has been guided by four major conceptual models. The models seek to explain the inevitable interaction between relatively stable temperamental structures and mental disorders. Theoretically, the four models differ with regards to assumptions of temporality and etiology; that is, *a)* the degree to which the pre-existence or occurrence of one affects the other at another point in time, and *b)* whether they are assumed to stem from the same underlying psychological and neurobiological factors.

Vulnerability model. The model most supported in the scientific literature is the *vulnerability model*. The vulnerability model posits that underlying temperamental traits evident early in life increase the likelihood of an individual later developing a mental disorder. In this model, temperament and psychopathology are seen as qualitatively distinct entities where temperament is the bedrock upon which pathology develops, thus assuming temporality. The vulnerability model is perhaps the most intuitive and has the longest and most extensive history of supporting evidence. Empirical literature links specific dimensions of temperament to distinct pathways of abnormal development and specific diagnostic categories (Clark & Watson, 1991; Jansen & Mathiesen, 2008; Watson, Gamez, & Simms, 2005; Windle & Windle, 2006). For example, a significant body of literature links dimensions of temperament with later substance use disorders. A study examining the stability, continuity, and association of adolescent temperament and early adult substance use disorders found increased rates of early adult substance use disorder to be associated with low adolescent task orientation and low flexibility

(Windle & Windle, 2006). Results from the Australian Temperament Project demonstrated that high negative reactivity, high sociability, and low persistence among 15-16 year-olds predicted later substance use (Williams et al., 2000). Neurobehavioral disinhibition at age 16 has also been linked with early-onset substance use disorder (SUD) assessed at age 19 (Tarter et al., 2003) with children high on disinhibition showing a six-fold increase in risk for SUD. Behavioral observations as early as age three have also been linked with psychiatric and substance use disorders in early adulthood with undercontrolled and inhibited three-year-olds showing elevated rates of alcohol problems and more suicide attempts at age 21 (Caspi et al., 1996).

The association between temperament, and anxiety and depressive disorders provides additional evidence supporting the vulnerability model. Kagan, Snidmen, Zentner, and Peterson (1999) examined infant reactivity and anxious symptoms at 7 years of age finding that infants classified as high in reactivity at 4 months were more likely to display anxious symptoms and were more accurate on a task requiring reflex inhibition. Another important study explored the long-term impact of adolescent difficult temperament on lifetime major depression assessed 20 years later among offspring at high-risk (one or more parent depressed) versus low-risk (no parent depressed) for depression (Bruder-Costello et al., 2007). The authors found that difficult temperament assessed in adolescence (*M* age = 16 years) predicted a three-fold increased risk for lifetime major depressive disorder at 20-year-follow-up. Analyses revealed a partial mediation of parental depression on offspring depression via offspring difficult temperament, which suggests that temperament may play a key role in the heritability of depression. Results also indicated a trending interaction whereby temperament was a more powerful predictor of lifetime MDD in low-risk rather than high-risk offspring. Conceptually, this study provides solid

evidence for the vulnerability model of the temperament-psychopathology link, and offers insight into differential effects of difficult temperament among high and low-risk offspring.

In addition to substance use disorders and internalizing disorders, early temperamental traits predict externalizing disorders as well. For example, ADHD has been linked with deficits in inhibitory control, high sensation and novelty seeking, extraversion, and low conscientiouness (see Nigg, 2006, for review), while conduct problems have been linked with high approach, combined with high negative reactivity (Frick & Morris, 2004) and low effortful control (Rothbart, 2007).

Spectrum/continuum model. The *spectrum/continuum model* posits that mental disorders are extreme variants of temperamental profiles. This model posits that temperament and psychopathology have a shared underlying structure and that taxonomic distinctions are artificial. Temporality is not necessarily assumed in this model. Research specifically examining the spectrum model may lie more appropriately in the psychobiological domain which can more clearly delineate underlying shared biological etiologies. However, while the aforementioned research supporting the vulnerability model has generally been interpreted as establishing the link between early temperamental traits and later acute mental disorders, these findings could arguably be interpreted in support of the spectrum model as well (Tackett, 2006). For example, early childhood traits of inhibition or shyness may be risk factors for later development of an anxiety disorder, but it can also be said that those who go on to develop anxiety disorders may have simply shifted along the continuum to the more severe end in adulthood. That is to say that the two models may not be mutually exclusive, but that there may be a predisposition which contributes to a spectral shift towards a pathological outcome.

More explicit evidence does exist, however, supporting the spectrum model. Psychobiological correlates including neurotransmitter functioning and psychophysiological measures associated with behavioral disinhibition (Electrodermal responding – EDR, cardiac pre-ejection period – PEP, respiratory sinus arrhythmia – RSA) have been associated with both temperament/personality functioning and acute behavioral disorders including Conduct Disorder and ADHD in children and adolescents (see Beauchaine, 2001). In addition, a prominent dimensional model linking mental disorders with temperamental traits is the Tripartite Model proposed by Clark & Watson (1991). The model seeks to explain the shared etiology of anxiety and depression which theoretically contributes to their significant comorbidity. Clark and Watson proposed that Negative Affect (general affective distress) is common to both anxiety and depression, while low Positive Affect is specific to depressive disorders, and high Physiological Hyperarousal is specific to anxiety-related disorders. This variant of the spectrum model helps explain the high co-occurrence of anxiety and depression and suggests that all persons move along a continuum of disordered or not disordered depending on their present level of NA, PA, or physiological arousal which vary due to an individual's biological composition.

Pathoplasty model. The *pathoplasty model* posits a significant temporal relationship between temperament and psychopathology, such that the presentation, course, and prognosis of a mental disorder are affected by the pre-existing temperament of the individual. A recent study explored child conduct problems and dimensions of temperament, as well as other risk factors (e.g., harsh parenting, child intelligence), fearlessness to frightening sound at age 2 was the only significant predictor of initial severity of conduct problems (age 2), and persistence of problems through age 8 (Shaw, Gilliom, Ingoldsby, & Nagin, 2003). This study provides evidence for the

pathoplasty model whereby a temperamental trait (i.e., reactivity) appears to affect the severity and persistence of conduct problems in children.

The pathoplasty model has additional support in a study examining factors that mediate the relationship between positive and negative emotionality on anhedonic depressive symptoms in a sample of 350 adolescents (Wetter & Hankin, 2009). The authors found that over a 5-month period dependent stressors mediated the relationship between baseline levels of NE and anhedonic depressive symptoms, while supportive relationships mediated the relationship between PE and anhedonic depressive symptoms. These findings begin to illustrate mechanisms through which temperament affects the presentation of depression in adolescents.

Scarring model. Similar to the pathoplasty model, the *scarring model* posits that psychopathology and temperament directly affect one another, except scarring refers to when an individual's temperament is permanently altered following the remission of an acute mental disorder. In this model temporality is again assumed as temperament is theorized to be permanently altered following an acute mental disorder. Yet, while there exists a dearth of evidence to support the pathoplasty model, virtually none exists in support of the scarring model.

The reason such scant evidence exists for these models is that examining the temporal relationship between temperament and psychopathology requires rigorous research methodology including longitudinal studies that assess relative changes in temperament and psychopathology, comparison of subjects with genetic vulnerabilities to healthy controls, and data pre- and post-first-onset major depression. Evidence does exist, for example, in a longitudinal study Shiner and colleagues (2002) found that antisocial behavior problems in childhood predicted an increase in negative emotionality (neuroticism) in adulthood after adjusting for childhood negative

emotionality. However, this relationship may have more to do with shared etiology than temporality and may be explained more aptly by the spectrum model.

None of these four models independently explain the temperament-psychopathology link and they are not necessarily mutually exclusive. It may be that 1) different models assume greater relevance at different stages of development, 2) some combination best explains the relationship, or 3) that different models explain different forms of psychopathology (Clark, 2005; Clark et al., 1994; Tackett, 2006). By understanding this relationship we can develop more accurate and efficient diagnostic and treatment strategies as well as prevention initiatives geared towards minimizing the impact of temperamental risk factors. As such, it is vital to test these models with scientific research in order to glean a clearer picture of the role of temperament in developmental psychopathology.

The Current Study

Most temperament research focuses on child and adolescent development. However, given its constitutional nature, temperament lends itself particularly well to exploration across the lifespan (Rothbart, Derryberry, & Hershey, 2000). The transition from adolescence to adulthood comes with increasing pressures of individuation, intimacy, and autonomy, and structural neuroimaging evidence confirms that the frontal lobe continues to develop well into the third decade of life (Conklin, Luciana, Hooper, & Yarger, 2007). In addition, this developmental period witnesses high rates of first onset mental illness. Therefore, it is important to examine the relationship between temperament and psychopathology during this critical period of development.

Pursuant of a deeper understanding of the relationship between temperament and psychopathology, the current study aims to examine the conceptual models of the temperament –

psychopathology link. Specifically, the study examines the pathoplasty model, which posits that underlying temperament affects the manifestation of mental illness– for example, the onset, course, and prognosis of a disorder. Validating this model is an important step towards developing a more thorough conceptualization of the temperament – psychopathology relationship. Yet, there exists scant evidence in support of the pathoplasty model because testing this model requires multivariate genetically-informed longitudinal study designs (Tackett, 2006). The current study largely satisfies these criteria and will examine the pathoplasty model over a 20-year period from adolescence to adulthood among offspring at high- and low-risk for depression with easy or difficult temperament.

The current study is a secondary data analysis from the original longitudinal High Risk Study examining the intergenerational transmission of depression (Weissman et al., 1987). Findings from over 25 years of data show that offspring of depressed parents (high-risk) are at threefold higher risk for lifetime major depression than offspring of non-depressed parents (low-risk) (Weissman et al., 1997, 2006). In addition, high-risk offspring show earlier onset of major depression, and poorer work, family, marital, and overall functioning (Weissman et al., 1997). However, environmental factors such as family discord and parental affectionless control more powerfully predict lifetime major depression among low-risk compared to high-risk offspring (Nomura et al., 2002; Pilowsky et al., 2006). This finding indicates a potential masking effect whereby the predisposition to depression among high-risk offspring is so strong that the adverse effects of a harmful environment are not as visible (i.e., predictive) as they are among low-risk offspring. Finally, results show that difficult temperament is significantly more prevalent in high-risk offspring and predicts lifetime MDD in both high and low-risk offspring (though the strength of this relationship is higher in low-risk offspring) (Bruder-Costello et al., 2007). Also,

temperament partially mediates the relationship between parental depression and offspring depression and is thus at least partly responsible for the heritability of depression (Bruder-Costello et al., 2007). However, an important limitation of this study is that the authors did not control for non-independence of outcome (i.e., "family effect"). That is, having multiple offspring from the same high-risk family artificially increases the chances of finding a significant association between parental depression, offspring depression, and difficult temperament (i.e., Type I error) due to shared biological and environmental factors. The current study will expand upon these findings by controlling for non-independence of outcome, and examining how parental depression and offspring temperament affect the clinical presentation of major depressive episodes.

In sum, this multivariate longitudinal familial study has provided a wealth of information regarding heritability, trajectory, and key correlates of major depression. However, all major depressive episodes cannot be considered equal and the clinical presentation may depend upon the constitutional makeup (i.e., temperament) of the individual. Therefore, a logical next step is to examine not just the presence or absence, but the *presentation* of major depression in relation to biologically-based factors such as temperament.

The current study will address this question by examining the relationship between temperament and lifetime major depression in offspring at high and low-risk for depression. This design offers the unique ability to examine the familial transmission of depression among two clinically diverse samples. The proposed study has two primary aims:

1) To provide supporting evidence for Bruder-Costello and colleagues (2007) while adjusting for non-independence of outcome (i.e., "family effect"), which could

significantly increase the chance of Type I error by considering offspring from the same parents at equal and independent risk.

   a. Hypothesis 1a: High-risk offspring will show significantly higher rates of lifetime MDD than low-risk offspring when adjusting for family effect.
   b. Hypothesis 1b: High-risk offspring will have more difficult temperament than low-risk offspring when adjusting for family effect. Specifically, high-risk offspring will show lower attention and adaptability, and greater irritability.
   c. Hypothesis 1c: Offspring with "difficult temperament" (determined by median split) will have higher rates of lifetime MDD than those with "easy temperament" when adjusting for family effect.

2) To examine the pathoplasty model of the relationship between temperament and psychopathology, specifically major depression. How does difficult temperament assessed during adolescence affect the frequency, intensity, and duration of major depressive episodes (MDE) across the lifespan? Does risk status (i.e., having at least one parent depressed) moderate this relationship?

   a. Hypothesis 2a: Offspring with difficult temperament at baseline will report more frequent, more intense, and longer lifetime MDEs on average than offspring with easy temperament.
   b. Hypothesis 2b: Risk status will moderate the relationship between difficult temperament and the frequency, intensity, and duration of MDEs such that difficult temperament will be more strongly related to the frequency, intensity, and duration of MDEs among low-risk, compared to high-risk offspring.

Methods

Participants

The original study sample consisted of depressed probands recruited from the Yale University Depression Research Unit and non-depressed probands recruited from a large epidemiological survey in the same community, and their offspring. The depressed probands had moderate to severe depression as assessed by the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L; Mannuzza, Fyer, Klein, & Endicott, 1986) requiring four-week duration of symptoms and significant impairment in psychosocial functioning; they had never been diagnosed with another mental disorder. The non-depressed probands were required to have no lifetime diagnosis of mental illness assessed in four separate interviews. All probands were Caucasian and group matched for age and sex and proband groups (depressed, non-depressed) did not differ by sex, age, number of marriages, education, religion, social class, or number of children in the family (see Weissman et al., 1987). The offspring of depressed and non-depressed parents were interviewed at up to four time points: Baseline (Wave 1), two years later (Wave 2), 10 years later (Wave 3), and 20 years later (Wave 4). At the time of first interview, the sample consisted of 220 offspring from 91 families, including 153 offspring with one or more depressed parent ("high-risk" offspring), and 67 offspring with neither parent depressed ("low-risk" offspring). By Wave 3, two offspring had died and one had been determined to have Down's Syndrome, reducing the total sample to 217; 202 of the 217 (93%) were interviewed at Wave 3. In the following ten years, another two participants died leaving 215 of the original 220 offspring; 173 of the 215 (80%) were interviewed again at Wave 4. The current sample is comprised of 203 offspring from 80 families

who completed 1) a diagnostic interview at Wave 1 and/or Wave 2 and again at Wave 3 and/or Wave 4, and 2) completed an assessment of temperament at Wave 1 or Wave 2.

Diagnostic Assessments

Offspring and parents were interviewed up to four times (Wave 1, Wave 2, Wave 3, Wave 4) using the SADS-L (Mannuzza, et al. 1986) for adults, and the K-SADS-E (Kaufman, Birmaher, Brent et al., 1997) for children age 6 to 17. For participants under age 18, both child and parent were interviewed about the child. For current study, only child self-report data were used. Trained doctoral and master's level mental health professionals conducted all interviews, and all interviewers were blind to lifetime diagnostic status of parent and child. Best estimate (BE) procedure (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982) was used to make all diagnoses at all waves. Best estimate procedure increases diagnostic accuracy and involves experienced clinicians making final diagnoses based upon blind review of multiple sources of data (e.g., clinical interview, family history, medical records). Best estimate diagnoses were made at each wave for lifetime and current diagnosis. At the initial baseline interview (wave 1 or wave 2) BE lifetime diagnoses were made to determine lifetime history of major depression prior to beginning the study. Subsequently, when participants missed a wave of data collection the following interview included assessment of any major depressive episodes (MDEs) that occurred during the interim. For example, if Subject A was interviewed at Wave 1, Wave 2, and Wave 4, the Wave 4 interview would include any MDEs in the roughly 18 years between Wave 2 and Wave 4, as well as any current diagnoses at Wave 4. If Subject B was interviewed at Wave 1, Wave 3, and Wave 4, the Wave 3 interview would include all depressive disorders in the 10 years between Wave 1 and Wave 3. In our final analyses, *lifetime diagnosis* refers to having at least one BE MDD diagnoses at any of the four waves.

Assessment of Temperament

Offspring completed the Dimensions of Temperament Scale (DOTS; Lerner et al., 1982) at Wave 1 or Wave 2. The DOTS is designed to assess dimensions of temperament related to psychosocial maladjustment. It is theoretically grounded in Thomas & Chess' seminal work in the NYLS whereby temperament is understood as the "how" of human behavior, rather than the "what" or "why." It is designed to demonstrate consistencies of behavioral style across situations. The DOTS consists of 34 items which represent five dimensions: 1) Activity Level (activity during sleep), 2) Attention span/distractibility (task persistence), 3) Adaptability/ approach-withdrawal (response to novel situations), 4) Rhythmicity (regularity of eating and sleeping habits), and 5) Irritability (reactivity to sensory stimuli, intensity of reaction to stimuli, and restlessness). The survey is self-report and requires a "true" or "false" response to each item. Example items include: "When a person comes towards me my first response is to move back." "Things going on around me can take me away from what I am doing." "I move a great deal in my sleep." Scoring involves recoding reverse-coded items and summing the total responses so a higher score reflects a more difficult temperament. In addition, subscale scores were used to examine specific dimensions of temperament independently. As per Thomas and Chess (1977; 1981) and other studies using the DOTS (e.g., Bruder-Costello et al., 2007), the median total temperament score (current study = 15) was used as a cutoff for categorical analyses; participants with a score ≥ 15 were designated as having a "difficult temperament" and those with a score < 15 were designated as having an "easy temperament." Similar to methodology from Bruder and colleagues (2007) a "baseline" temperament score was then created using Wave 1 data when available and Wave 2 data for subjects who did not complete a

Wave 1 assessment of temperament. Of the 203 study participants, 155 completed the DOTS at Wave 1, and 48 completed the DOTS at Wave 2.

Presentation of Major Depression

In order to examine the pathoplasty model – Best Estimate data on frequency, intensity, and duration of lifetime Major Depressive Episodes (MDE) were compiled across the four waves to create three continuous outcome variables. However, the first wave of data collection for the original High Risk Study began over 25 years ago and given the broad study aims and the scientific evolution of diagnostic assessments over this time period, there were several data management pitfalls to overcome while creating these variables for the current study.

Frequency. Total number of MDEs was derived from summing the number of reported lifetime MDEs. Diagnostic data from Waves 1 and 2 included current and lifetime diagnoses of major depression. For participants who did not complete a Wave 1 interview, the Wave 2 interview served as a baseline interview and assessed the number of lifetime MDEs prior to entering the study. At Wave 3 (10-years) and Wave 4 (20-years) subjects were asked to report the number of MDEs occurring during the interim 10 years. For participants who completed Wave 4 interview but not Wave 3, data included number of MDEs since previous interview (i.e., baseline). Total number of lifetime MDEs was then standardized by dividing the total number by the number of years in the study. For participants who only completed the study through Wave 3 the total number of lifetime MDEs was divided by 10 (the average number of years at Wave 3 follow-up), while for those who completed the study through Wave 4 the total number of MDEs was divided by 20 (the average number of years at Wave 4 follow-up). This procedure was used to standardize the total number of MDEs by accounting for the number of years in the study (i.e., those with an additional 10 years in the study have a greater chance of having

additional MDEs). Participants who missed one of the middle waves (Wave 2 or Wave 3) but completed Wave 4 are still considered 20-year participants since missing diagnostic data was accounted for during clinical interview at Wave 4.

Severity. Severity of MDEs was assessed at each wave and an Average Worst Severity variable was created to examine intensity of depression among depressed offspring. The initial goal was to derive an average severity score by summing severity ratings for each lifetime MDE and dividing by the total number of MDEs for each offspring. However, the scientific evolution of assessment tools and methodological constraints rendered this goal unattainable. For example, severity ratings at each wave differed with regards to recording procedures and scale variability. At Waves 1 and 2 severity of current episode (if present), and most severe lifetime MDE was assessed. At Wave 3, severity of each MDE was assessed, and at Wave 4 severity of worst episode between Wave 3 and Wave 4 was again assessed. In other words, Waves 1, 2, and 4 were similar in that they each assessed severity of the worst past MDE since previous interview (or lifetime) and current episode severity, if present, while Wave 3 assessment included severity ratings for each MDE reported during that interview. The Wave 3 method would have provided the appropriate data for deriving an overall average severity rating were it used at all other waves. Due to these methodological limitations, overall average severity could not be ascertained. However, an Average Worst Severity variable was created by taking the most severe MDE from each wave and obtaining the average. Additionally, severity ratings had to be recoded for consistency. Waves 1 and 2 were recoded to match the unit of measurement used at Waves 3 and 4. Waves 1 and 2 used a 7-point Likert scale (1 = None, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Severe, 6 = Extreme, 7 = Catastrophic), while Waves 3 and 4 used a 3-point Likert scale (1 = Mild, 2 = Moderate, 3 = Severe). Wave 1 and Wave 2 severity data were

recoded as follows: 1 (None) through 3 (Mild) were recoded as 1 = Mild; a score of 4 (Moderate) was recoded as 2 = Moderate; and 5 (Severe) through 7 (Catastrophic) were coded as 3 = Severe. Resultant severity averages range from 1 = Mild, 2 = Moderate, and 3 = Severe. Using a 7-point Likert scale at all waves would have provided more variability and thus more robustness, but given the 3-point scale used at Waves 3 and 4, the best option was to recode the 7-point ratings to create the same unit of measurement. The alternative of using standardized z-scores was explored and analyses re-ran, but results did not differ.

Duration. Duration for each reported MDE was also assessed at each study wave. Duration of episodes was recorded in weeks for Waves 1-3, and in days at Wave 4. All durations were recoded into days for consistency. Durations of all reported MDEs across all waves were then summed for each participant and divided by number of reported lifetime MDEs producing the final outcome variable Average Duration of MDEs. This procedure accounted for missing data because each participant's score reflects their unique number of lifetime MDEs whether they complete through Wave 3 or Wave 4. Participants with a greater number of MDEs will theoretically have a more accurate average duration score because they have more data points than those with only one or two lifetime MDEs. Nevertheless, the derivation of this variable is appropriate given the complexity of the dataset.

Data Analytic Plan

Data analyses were conducted to test the pathoplasty model of the association between temperament and major depressive disorder. This involved a two-stage procedure. Study Aim 1: The first stage was a confirmatory analysis of Bruder-Costello and colleagues (2007) with the important additional step of adjusting for family effect (i.e., non-independence of outcome). This involved examining the association of both parental MDD and offspring temperament with

offspring lifetime MDD. First, total temperament scores and dimension scores were compared between high-risk and low-risk offspring using Analysis of Covariance (ANCOVA) that adjusted for offspring age at time of baseline assessment. Mixed Model procedures were then used to compare the two offspring risk groups on temperament scores while adjusting for nested family effect in addition to age at baseline. Second, the association between parental MDD and both offspring MDD and offspring difficult temperament (dichotomized into easy vs. difficult) was tested using Logistic Regression that adjusted for offspring age at baseline. In following, Generalized Estimating Equations (GEE) were used to test these associations while controlling for family effect in addition to baseline age. Third, the association between difficult temperament and offspring lifetime MDD was tested using Logistic Regression that adjusted for age at baseline. Again, GEE was used to test this association while adjusting for family effect in addition to offspring age. It should be noted that the current sample includes 34 participants who entered the study and completed a baseline diagnostic interview at Wave 2. This differed from Bruder-Costello and colleagues (2007) who only examined the 169 participants with a Wave 1 baseline diagnostic interview. This important note precludes strict confirmatory conclusions about the impact of controlling for family effect, as the study samples are not identical.

Study Aim 2: The second stage of data analysis involved statistical tests examining the pathoplasty model. Specifically, Mixed Model procedures were used to examine the association between difficult temperament, offspring risk status, and the clinical presentation of Major Depressive Episodes (MDE). For each of the following outcomes – total number of lifetime MDEs, average worst severity of MDEs, and average duration of MDEs – Mixed Model procedures were used to examine these associations while adjusting for baseline age and nested family effect. For each outcome, three models were run: Model 1 - Temperament as lone

predictor, Model 2 - Risk Status as lone predictor, and Model 3 - an interaction model with Temperament, Risk Status, and Temperament X Risk Status interaction term.

Results

Participants

The current study includes data from 203 offspring (from 80 families) who completed a diagnostic interview at Wave 1 and/or Wave 2, and subsequently at Wave 3 and/or Wave 4, and an assessment of temperament at Wave 1 or Wave 2. Fifty-six percent were female. One hundred sixty-nine participants completed a Wave 1 diagnostic interview and 34 completed an initial diagnostic interview at Wave 2 yielding a total baseline sample of 203. There were no significant differences in sex, level of education, household income, or religious beliefs between those who completed an initial interview at Wave 1 and those who competed an initial interview at Wave 2. However, participants with initial interview at Wave 1 were more likely to be younger and single/never married than those initially interviewed at Wave 2. Of the 203 participants, 202 completed the study through Wave 3 (10 years) and 173 completed the study through Wave 4 (20 years). There were no significant differences in age, marital status, household income, religious beliefs, or highest level of education between those who completed through Wave 4 and those who dropped out after Wave 3. However, women were more likely than men to complete the study through Wave 4 ($X^2 = 14.4$, $p < .01$).

Table 1
Descriptives for entire sample and by risk group

	Entire Sample (N = 203)	High Risk (n = 138)	Low Risk (n = 65)
Age[1] M(SD)	18.7(6.5)	19.2(6.9)	17.6(5.6)
	N (%)	N (%)	N (%)
Sex[1]: Female	114(56)	79(57)	35(54)
Male	88(43)	58(42)	30(46)
Marital Status[2]			
Married	113(56)	74(54)	39(60)
Never married	61(30)	43(31)	18(28)
Separated/divorced	27(13)	20(14)	7(11)
Highest level of education[2]			
No high school diploma	7(3.5)	5(4)	2(3)
High school diploma	54(27)	37(27)	17(26)
Tech school or 2-yr college	57(28)	37(27)	20(31)
Four-year college	56(27)	42(30)	14(22)
Graduate/professional	29(14)	17(12)	12(18)
Religious affiliation[2]			
Roman Catholic	120(59)	75(54)	45(69)
Protestant	31(15)	25(18)	6(9)
Jewish	9(4.4)	5(4)	4(6)
Personal religious	15(7.4)	9(7)	6(9)
Agnostic/atheist	4(2)	4(3)	0(0)
Other	18(9)	15(11)	4(6)
Household Income[2]			
<$30,000	48(24)	37(27)	11(17)
30,000 – 49,000	44(22)	30(22)	14(21)
50,000 – 89,000	56(27)	38(27)	18(28)
90,000 or greater	52(26)	31(22)	21(32)

[1] Assessed at initial interview (Wave 1 or 2)
[2] Assessed at last interview (Wave 3 or 4)

One-hundred fifty-five participants completed the DOTS at Wave 1, while the remaining 48 completed the DOTS at Wave 2. These initial DOTS interview data were combined and used as the baseline assessment of temperament. Offspring who completed the DOTS at Wave 2 were significantly older ($M = 25$, $SD = 8.0$) than those who completed the DOTS at Wave 1 ($M = 17$, $SD = 4.5$; $p < .001$); there were no significant differences between these groups on demographic variables of level of education, marital status, household income, or religious affiliation. Combined, mean age at baseline interview was 18.6, $SD = 6.5$. The study sample of 203 offspring is comprised of 138 high-risk offspring and 65 low-risk offspring. There were no significant differences in age, sex, marital status, religion, household income, or level of education between high and low-risk offspring (see Table 1 for full demographics). A Pearson correlation matrix displays unadjusted relationships between all variables in analyses (Table 2).

Table 2
Pearson correlations among all variables for entire sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1) Age	1													
2) Sex	-.16*	1												
3) Education Level	-.07	-.04	1											
4) Household Income	.10	.01	.31**	1										
5) Risk Status	.11	-.02	-.02	-.12	1									
6) Difficult Temperament	-.20**	.02	-.16*	-.07	.16*	1								
7) Lifetime MDD	.21**	-.13	-.14*	-.07	.32**	.18**	1							
8) Frequency MDEs	.06	-.00	-.01	-.35**	.03	.30**	[a]	1						
9) Duration MDEs	.23*	.03	-.15	-.31**	.05	-.14	[a]	.15	1					
10) Severity MDEs	.05	.05	-.03	-.15	-.11	-.21*	[a]	.11	.34**	1				
11) DOTS Activity	-.19**	.06	-.08	-.05	.06	.56**	-.01	.17	.00	-.22*	1			
12) DOTS Attention	-.12	-.11	.01	.09	.08	.71**	.17*	.03	-.30**	-.22*	.21**	1		
13) DOTS Adaptability	.14*	.03	-.11	-.11	.14*	.36**	.06	.21*	.22*	.03	.11	.11	1	
14) DOTS Rhythmicity	-.22**	.07	-.07	-.02	.07	.62**	.13	.27**	-.19	-.10	.24**	.24**	-.08	1
15) DOTS Irritability	-.17*	.08	-.28**	-.22**	.09	.51**	.13	.18	.04	-.03	.27**	.10	.01	.27**

**$p < .01$, *$p < .05$
[a] Not computed because Lifetime MDD is constant.

Aim 1

Confirming the association between parental depression, offspring depression, and offspring temperament. Mean subscale scores and total difficult temperament scores on the DOTS for high- and low-risk offspring adjusting for baseline age are provided in Table 3. High-risk offspring show significantly greater difficult temperament (M = 15.7, *s.e.* = 0.46) than low-risk offspring (M = 13.5, *s.e*. = 0.68), $F(1, 199) = 7.20$, $p < .01$. Results also indicate trends that high-risk offspring scored higher on dimensions of Attention ($p = .10$), Adaptability ($p = .07$), and Irritability ($p = .10$) than low-risk offspring. This suggests a behavioral style of being easily distracted, withdrawing from novel stimuli, and becoming easily irritated. When adjusting for family effect in addition to baseline age (Table 4), high-risk offspring continue to show higher rates of overall difficult temperament (M = 15.7, s.e. = 0.53) than their low-risk counterparts (M = 13.7, s.e. = 0.78), $F(1, 199) = 5.30$, $p < .05$, as well as a similar trend for the dimension of Adaptability (p = .07). Trends for Attention and Irritability are no longer found. These results suggest that having multiple offspring from the same family does not significantly weaken the statistical relationship between parental depression and offspring temperament.

Table 3
ANCOVA examining the association of Parental MDD with Offspring Temperament scores adjusting for Baseline Age

	Parental MDD		
DOTS (N = 203)	Low Risk (n = 65)	High Risk (n = 138)	
	Mean (s.e.)	Mean (s.e.)	F
Difficult Temperament	13.5 (0.68)	15.7 (0.46)	7.20**
Activity	1.3 (0.18)	1.6 (0.12)	1.58
Attention/distractibility	4.3 (0.35)	4.9 (0.24)	2.17+
Adaptability/approach-withdrawal	1.9 (0.21)	2.4 (0.15)	3.38++
Rhythmicity	3.9 (0.27)	4.3 (0.18)	2.04
Irritability	2.0 (0.20)	2.4 (0.14)	2.51+

**$p < .01$, ++$p = .07$, +$p = .10$

Table 4
Mixed Model Analyses examining the association of Parental MDD and Offspring Temperament adjusting for Baseline Age and Family Effect

	Parental MDD		
DOTS (N = 203)	Low Risk (n = 65)	High Risk (n = 138)	
	Mean (s.e.)	Mean (s.e.)	F
Difficult Temperament	13.5 (0.78)	15.7 (0.53)	5.30*
Activity	1.3 (0.18)	1.6 (0.12)	1.30
Attention/distractibility	4.3 (0.35)	4.9 (0.24)	2.00
Adaptability/approach-withdrawal	1.9 (0.23)	2.4 (0.16)	3.36++
Rhythmicity	3.9 (0.33)	4.3 (0.22)	1.20
Irritability	2.0 (0.23)	2.4 (0.16)	2.11

*$p < .05$, ++$p = .07$

Tables 5 and 6 show the association between parental MDD (i.e., offspring risk status) and 1) offspring lifetime MDD, and 2) offspring temperament (dichotomized into "easy" vs. "difficult"). Table 5 adjusts for baseline age, while Table 6 adjusts for baseline age and family effect (i.e., non-independence of outcome). As predicted and shown in Table 5, high-risk offspring have significantly higher rates of lifetime MDD than low-risk offspring, OR = 4.0, 95% CI [2.1, 7.7], when adjusting for offspring age. When adjusting for family effect as well as age (Table 6), high-risk offspring continue to show higher rates of MDD than low-risk offspring, OR = 4.0, 95% CI [2.0, 8.0]. Also shown in Tables 5 and 6 is the relationship between parental MDD and offspring temperament. Results indicate that high-risk offspring have significantly higher rates of "difficult" temperament when adjusting for age alone, OR = 2.1, 95% CI [1.1, 3.8] (see Table 5) and when adjusting for family effect as well as age, OR = 2.1, 95% CI [1.1, 3.9] (see Table 6). The relationship between parental MDD on offspring lifetime MDD when adjusting for family effect remains significant at $p < .001$. In addition, parental MDD continues to predict offspring temperament at $p < .05$ also when adjusting for family effect and age.

Table 5
Logistic Regression Models: Parental MDD predicting Lifetime MDD and Difficult Temperament in offspring adjusting for baseline age

	Parental MDD			
	Low Risk (n = 65) n(%)	High Risk (n = 138) n(%)	Wald	OR (95% CI)
(1) Lifetime MDD	18(28)	85(62)	17.4***	4.0 (2.1, 7.7)
(2) Difficult Temperament	27(42)	79(57)	5.4*	2.1 (1.1, 3.8)

****p* < .001, **p* < .05

Table 6
Generalized Estimating Equations: Parental MDD predicting Difficult Temperament and Lifetime MDD adjusting for baseline age and family effect

	Parental MDD			
	Low Risk (n = 65) n(%)	High Risk (n = 138) n(%)	Wald	OR (95% CI)
(1) Lifetime MDD	18(28)	85(62)	15.3***	4.0 (2.0, 8.0)
(2) Difficult Temperament	27(42)	79(57)	5.0*	2.1 (1.1, 3.9)

****p* < .001, **p* < .05

Using the same sequence of analyses, we examined the relationship between difficult temperament and offspring lifetime MDD first adjusting for age (Table 7) then adjusting for age and family effect (Table 8). Offspring with difficult temperament had higher rates of lifetime MDD than low risk offspring when adjusting for baseline age alone, OR = 2.0, 95% CI [1.1, 3.6], and when adjusting for family effect and age together, OR = 2.0, 95% CI [1.1, 3.6].

Table 7
Logistic Regression: Difficult temperament predicting Lifetime MDD adjusting for baseline age

	Temperament			
	Easy (n = 97) n(%)	Difficult (n = 106) n(%)	Wald	OR (95% CI)
(1) Lifetime MDD	42 (43)	61(58)	6.3*	2.1 (1.2, 3.8)

*$p < .05$

Table 8
Generalized Estimating Equation: Difficult temperament predicting Lifetime MDD adjusting for Age at Baseline interview and Family Effect (non-independence of outcome)

	Temperament			
	Easy (n = 97) n(%)	Difficult (n = 106) n(%)	Wald	OR (95% CI)
(1) Lifetime MDD	42 (43)	61(58)	6.2*	2.1 (1.2, 3.8)

*$p < .05$

Combined, the results from Aim 1 of the study are important for two reasons. First, as shown in Tables 3 and 4, it is important to adjust for family effect as the relationship between parental depression and overall offspring temperament score is weakened, and trends on dimensions of attention and irritability are no longer present. However, Tables 5 – 8 largely confirm that the relationship between parental MDD, offspring MDD, and offspring temperament are not better explained by non-independence of outcome (i.e., children with the same biological predisposition). These findings suggest that while offspring from the same family cannot be considered independent of one another given their shared environmental and biological circumstances, there remains a powerful association between parental depression and offspring temperament.

Aim 2

The following analyses were conducted to examine the pathoplasty model of the temperament-psychopathology link. That is, how does temperament affect the *presentation* of major depression? Specifically, to provide a more nuanced understanding of the relationship between temperament and major depression data on the frequency, severity, and duration of Major Depressive Episodes (MDE) among offspring with at least one lifetime MDE were explored. Due to positively skewed distribution (Skewness = 4.6, Kurtosis = 25) (see Figure 1) log linear transformation was used for dependent variable "Average Duration."

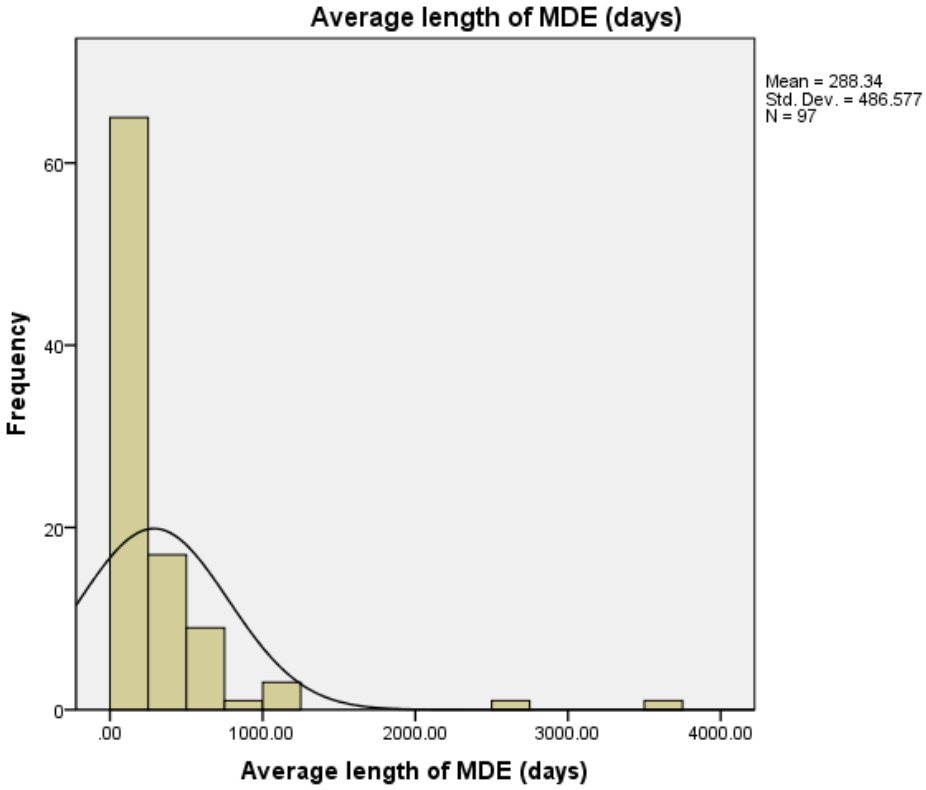

Figure 1. Distribution of average length of major depressive episodes.

Several interesting results were found and are shown in Table 9. Offspring with difficult temperament have significantly more lifetime MDEs per study year (M = 0.17, SD = .12) than

those with an easy temperament (M = 0.13, SD = .08), $F(1, 94) = 4.00$, $p < .05$. Moreover, difficult temperament continues to show a trend in predicting lifetime MDEs in Model 3 when the variables Risk Status and the interaction term (Risk X Temp) are included, $F(1, 92) = 3.27$, $p = .07$. Difficult temperament does not predict average duration or average worst severity of MDEs. However, risk status appears to moderate the relationship between temperament and severity of MDEs, $F(1, 87) = 4.06$, $p < .05$. Follow-up mixed model analyses adjusting for offspring age and family effect revealed a marginally significant effect among high-risk offspring, $F(1, 73) = 3.6$, $p = .06$, but no effect among low-risk offspring. More specifically, among high-risk offspring those with an easy temperament reported more severe MDEs (M = 2.4, SD = .54) than those with a difficult temperament (M = 2.1, SD = .65); among Low-Risk offspring there was no significant difference in severity score between offspring with easy vs. difficult temperament. This result is the opposite of what was predicted in Hypothesis 2b. However, the mean severity scores within the easy and difficult temperament groups across risk status are in the opposite direction which may account for the significant interaction effect. In addition, with such small N's particularly in the low-risk group it is difficult to obtain adequate power to draw firm conclusions at this time.

As a methodological check, analyses were run using temperament as a continuous variable rather than categorical variable. Results can be found in Table 10 and indicate a significant relationship between overall temperament score, and frequency and severity of MDEs. Higher overall temperament score predicted greater frequency of MDEs, but interestingly, predicted decreased severity of MDEs. In addition, the interaction effect predicting severity is no longer significant when temperament is assessed continuously.

Table 9

Mixed Models analyses examining how Difficult Temperament and Risk Status predict Frequency, Duration, and Severity of Lifetime Major Depressive Episodes adjusting for family effect and baseline age

		Total # MDEs per study year (N = 97)		Average Duration MDE [a] (N = 97)		Average Worst Severity (N = 92)	
Model 1		M (SD)	F	M (SD)	F	M (SD)	F
Temperament	Easy (n = 37)	.13 (.08)	4.00*	5.1 (1.0)	0.90	(n=35) 2.4 (.57)	1.97
	Difficult (n = 60)	.17 (.12)		4.8 (1.4)		(n=57) 2.2 (.64)	
Model 2							
Risk Status	Low (n = 17)	.15 (.08)	0.12	4.8 (1.2)	0.35	(n=16) 2.4 (.60)	1.23
	High (n = 80)	.16 (.11)		4.9 (1.3)		(n=76) 2.2 (.62)	
Model 3							
Temperament		--	3.27+	--	0.58	--	0.09
Risk Status		--	0.04	--	0.48	--	0.55
Temperament x Risk Status		--	0.21	--	0.01	--	4.06*
Low Risk	Easy (n = 8)	.11 (.06)	--	5.0 (1.1)	--	(n=7) 2.2 (.70)	n.s.
	Difficult (n = 9)	.18 (.09)		4.6 (1.3)		(n=9) 2.6 (.50)	
High Risk	Easy (n = 29)	.13 (.09)	--	5.1 (1.0)	--	(n=28) 2.4 (.54)	p = .06
	Difficult (n = 51)	.17 (.12)		4.8 (1.4)		(n=48) 2.1 (.65)	

*$p < .05$, +$p = .07$

[a] Log linear transformation adjusting for positive skew.

Table 10
Mixed Models analyses examining how Difficult Temperament (measured continuously) and Risk Status predict Frequency, Duration, and Severity of Lifetime Major Depressive Episodes, adjusting for family effect and baseline age

	Total # MDEs per study year (N = 97)	Average Duration MDE[a] (N = 97)	Average Worst Severity (N = 92)
Model 1	B	B	B
Difficult Temperament	.007**	-.033	-.025*
Model 2			
Risk Status	-.010	-.213	.190
Model 3			
Difficult Temperament	.007+	-.096+	-.002
Risk Status	-.012	1.74	-.563
Temperament[b] x Risk Status	-.000	.068	-.024

**$p < .01$, *$p < .05$, +$p < .10$
[a] Log linear transformation adjusting for positive skew
[b] Centered to reduce possible multicollinearity

It is also notable that Risk Status does not significantly predict any of the three outcomes in these analyses. Despite the strong relationship between parental MDD and offspring MDD found in Aim 1 of this study, as well as in previous studies with this high-risk sample (see Weissman et al., 1987, 1997, 2006), parental MDD does not appear to impact the presentation of depression (i.e., frequency, severity, duration), but rather, only the presence or absence of lifetime MDD.

Exploratory analyses

As a follow up to Aim 2, exploratory analyses examined the relationship between the five dimensions of temperament assessed by the DOTS (Activity, Attention/Distractibility, Adaptability, Rhythmicity, Irritability) and frequency, severity, and duration of MDEs. Using a

Mixed Model procedure separately for each outcome, all five dimensions were entered while adjusting for family effect and baseline age. Results are found in Table 11 and indicate that dimensions of Rhythmicity (b = .016, $p < .01$) and Adaptability (b = .014, $p < .05$) significantly predicted total number of MDEs per study year. Next, Attention/distractibility significantly predicted average duration of MDEs (b = -.116, $p < .05$). Finally, Activity predicted average worst severity of MDEs (b = -.093, $p < .05$) and Attention was marginally significant in predicting average worst severity (b = -.044, $p < .07$).The same analyses were then run separately for high risk (see Table 12) and low risk (see Table 13) offspring. Results indicate that among high-risk offspring Adaptability (b = .013, $p < .05$) and Rhythmicity (b = .016, $p < .01$) significantly predict frequency of MDEs, Attention/distractability marginally predicts average duration (b = -.101, $p < .07$), and Activity marginally predicts average worst severity (b = -.094, $p < .07$). Findings differ somewhat among low-risk offspring. For low-risk offspring, Rhythmicity alone predicts frequency of MDEs (b = .024, $p < .05$), Attention/distractability marginally predicts duration (b = -.387, $p < .07$), and Attention/distractability (b = -.174, $p < .05$) significantly predicts average worst severity, while Rhythmicity (b = .146, $p < .07$) marginally predicts average worst severity. In sum, these findings suggest a more nuanced relationship between temperament and major depression whereby individual dimensions of temperament predict qualitatively distinct aspects of major depressive episodes, and that these relationships differ for offspring at high and low risk for depression.

Table 11

Mixed Model analyses examining the association between dimensions of temperament and Total Number, Average Duration, and Average Worst Severity of MDEs among entire sample adjusting for baseline age and family effect

N = 203	Total MDEs	Average Duration	Worst Severity
	B (s.e.)	B (s.e.)	B (s.e.)
Activity	.009 (.007)	.004 (.08)	-.093 (.05)*
Attention/distractibility	-.003 (.004)	-.116 (.04)*	-.044 (.02)+
Adaptability	.014 (.006)*	.010 (.07)	.012 (.03)
Rhythmicity	.016 (.005)**	-.051 (.06)	-.007 (.03)
Irritability	.008 (.007)	.071 (.08)	.021 (.04)

**$p < .01$, *$p < .05$, +$p < .07$

Table 12

Mixed Model analyses examining the association between dimensions of temperament and Total Number, Average Duration, and Average Worst Severity of MDEs among low risk offspring adjusting for baseline age and family effect

Low Risk (n = 65)	Total MDEs	Average Duration	Worst Severity
	B (s.e.)	B (s.e.)	B (s.e.)
Activity	-.025 (.004)	-.252 (.268)	-.127 (.111)
Attention/distractibility	-.018 (.011)	-.387 (.176)+	-.174 (.070)*
Adaptability	.008 (.013)	-.080 (.186)	-.061 (.088)
Rhythmicity	.024 (.010)*	.031 (.170)	.146 (.066)+
Irritability	-.030 (.020)	-.391 (.318)	-.170 (.130)

*p < .05, +p < .07

Table 13

Mixed Model analyses examining the association between DOTS dimensions of temperament and Total Number, Average Duration, and Average Worst Severity of MDEs among High Risk offspring adjusting for baseline age and family effect

High Risk (n = 138)	Total MDEs	Average Duration	Worst Severity
	B (s.e.)	B (s.e.)	B (s.e.)
Activity	.014 (.008)	-.006 (.102)	-.094 (.052)+
Attention/distractibility	-.004 (.005)	-.101 (.055)+	-.031 (.028)
Adaptability	.013* (.006)	.108 (.077)	.028 (.038)
Rhythmicity	.016** (.005)	-.051 (.064)	-.018 (.032)
Irritability	.008 (.008)	.078 (.097)	.004 (.050)

*$p < .05$, +$p < .07$

Discussion

The current study examined the relationships between parental depression, offspring depression, and offspring temperament among 203 offspring at high or low-risk for depression. Offspring were followed over a 20-year study period. Two primary study aims were addressed. First, we sought to build upon Bruder-Costello and colleagues (2007) by confirming that parental depression predicts *a)* offspring lifetime depression and *b)* offspring difficult temperament while adjusting for non-independence of outcome (family effect), as well as confirming that *c)* offspring difficult temperament predicts offspring major depression also adjusting for family effect. Second, we sought to examine the *pathoplasty model* of the relationship between temperament and psychopathology by examining how offspring difficult temperament affects qualitative features of major depression – specifically, frequency, severity, and duration.

Study Aim 1

Results demonstrate that parental depression predicts offspring difficult temperament (measured continuously) and that high-risk offspring have a different temperamental profile than low-risk offspring. Specifically, high-risk offspring have more difficult temperament than low-risk offspring and display a temperamental profile that includes being more easily distracted, having difficulty adapting to new situations, and showing greater irritability. When adjusting for family effect the relationship between parental depression and offspring temperament is diminished but remains significant. High-risk offspring continue to display overall more difficult temperament than low-risk offspring, as well as lower adaptability. However, trends on dimensions of attention/distractibility and irritability are no longer present. These findings largely confirm the overall conclusion from Bruder-Costello and colleagues (2007) that parental depression predicts offspring difficult temperament. However, as expected the results indicate

that family effect (non-independence of outcome) does account for a portion of the variance. The weakened (though still significant) relationship highlights an important limitation in Bruder-Costello and colleagues (2007), who used the same data as the current study but did not adjust for non-indepedence of outcome. Non-independence of outcome refers to offspring from the same family are "dependent" on the same environmental (e.g. parenting) and biological (e.g. genetic) factors, and thus at greater likelihood of displaying similar outcomes. Nevertheless, when adjusting for family effect in our study we found parental depression continued to predict overall difficult temperament.

Additional analyses from aim 1 of the current study examined the relationship between parental depression and offspring depression, as well as parental depression and offspring temperament dichotomized into easy and difficult categories. These results illustrate that parental depression strongly predicts offspring lifetime depression even when adjusting for random family effect. High-risk offspring are four-times as likely as low-risk offspring to have at least one lifetime major depressive disorder (MDD). Parental depression also predicts offspring difficult temperament when adjusting for family effect such that high-risk offspring are twice as likely as low-risk offspring to have a difficult temperament. Lastly, results indicate that difficult temperament predicts lifetime MDD such that offspring with a difficult temperament are two times more likely to experience a lifetime MDD than offspring with an easy temperament. In sum, adjusting for random family effect does not have a major impact when examining *a)* the relationship between parental depression and offspring depression, or *b)* the relationship between parental depression and offspring temperament assessed dichotomously. Nor does family effect significantly impact the relationship between offspring temperament and offspring depression. The relationship between parental depression and offspring depression is well established and

strong (see Weissman et al., 1997, 2006) so we expected these findings to hold true when properly correcting for non-independence of outcome. Likewise, the construct of difficult temperament has been linked with essentially all forms of psychopathology including depression (Watson et al., 2005; Wetter & Hankin, 2009), anxiety (Kagan et al., 1999; Watson et al., 2005), substance abuse (Williams et al., 2000; Windle & Windle, 2006), externalizing behavior problems (Frick & Morris, 2004; Rettew et al., 2004; see Rothbart 2007), and bipolar disorder (Singh et al., 2008) so we would expect this result to retain its power as well.

Combined, these results provide corroborating evidence that parental depression predicts both offspring difficult temperament and offspring lifetime MDD, and that offspring difficult temperament predicts offspring lifetime MDD. In support of Bruder-Costello and colleagues (2007) these relationships are remarkably strong and sustained even when adjusting for random family effect.

Study Aim 2

The second aim of the current study was to examine the pathoplasty model of the relationship between temperament and psychopathology among offspring at high or low risk for depression. That is, how does temperament affect the presentation of major depression? Results from study aim 2 revealed important relationships among difficult temperament and qualitative indicators of major depression. Regardless of risk status, offspring with a difficult temperament had more frequent major depressive episodes (MDEs) than offspring with an easy temperament. Difficult temperament did not predict greater severity or longer duration of MDEs. These findings suggest that difficult temperament not only puts an individual at increased risk for depression (Aim 1) but also puts them at risk for having recurrent episodes over the lifetime.

With regards to risk status, having a depressed parent did not independently impact frequency, severity, or duration of MDEs. This is quite notable given the strength of the relationship between parental depression and offspring depression, and suggests parental depression predicts presence of offspring depression, but the quality of depression is more reflective of an individual's temperament.

While there was no main effect of temperament or risk status on severity of MDEs there was a significant interaction effect between risk status and temperament. Risk status moderated the relationship between temperament and severity of MDEs such that among high-risk offspring, those with an easy temperament reported more severe MDEs than those with a difficult temperament. This finding runs counter to our hypothesis that moderation would occur among low-risk offspring, which was based upon previous results from the High Risk Study (Nomura et al., 2002; Pilowsky et al., 2006) demonstrating a masking effect whereby a predisposition for depression (i.e., high-risk status) masks the impact of other potentially significant contributing factors (e.g., family conflict, parenting style). That is to say, the biological predisposition towards depression is so powerful in predicting offspring depression that environmental factors have less of an impact among high-risk offspring. However, given that temperament and risk status both have a significant biological component it may be more plausible that temperament would more strongly affect the quality of depression among high-risk offspring. This would reflect what could be coined 'double-dip' risk status whereby high-risk offspring with a difficult temperament would be expected to display more severe, longer, and more frequent episodes. However, this was not the case, rather, it was high-risk offspring with an easy temperament that reported greater severity. These findings suggest that temperament and predisposition to depression may share *some* biological etiology, but that other biological

and environmental factors are also likely at play. In other words, shared components may predict frequency of depressive episodes, but distinct factors may predict presentation of depression.

Genetic research informs this discussion as well. Research on the serotonin transporter gene 5-HTT has shown that carriers of the short allele are at greater risk for depression and anxiety-related temperamental traits (Pezawas et al., 2005) and anxious temperament has been linked with risk for depression (see Wong & Licinio, 2001). Short-allele carriers are also more vulnerable to environmental stressors showing more severe depressive symptomology in response to stressful life events (SLE) than individuals with at least one long allele (Caspi et al., 2003). We can assume then that high-risk offspring are more likely to be short-allele carriers and thus at greater risk for depression and anxious temperament. Our results do indicate more depression and more difficult temperament among high-risk offspring. But why then would easy temperament be related to more severe episodes among high-risk offspring? It may be that easy-temperament high-risk offspring had more SLE than difficult-temperament high-risk offspring, a factor not accounted for in this study. In addition, other candidate genes may be responsible for different temperamental traits such as attention, adaptability, rhythmicity which also may affect the quality of depression.

A third explanation may be that the relationship between offspring temperament and major depression is opposite for those at high and low risk. As shown in Table 9, the mean worst severity scores for easy vs. difficult offspring across risk groups are in opposite directions. The slopes are orthogonal which is why we do not see any main effects, but find a significant interaction. This possibility highlights the importance of comparing biologically disparate groups. As shown, difficult offspring do have more frequent episodes, which may “desensitize”

them to depression resulting in lower subjective reports of distress. Offspring with an easy temperament are less sensitized to depression and may perceive their episodes as very disruptive and more severe. We ran the same analyses using temperament as a continuous predictor (thus retaining all the variability) and found that more difficult temperament is actually associated with decreased severity of MDEs and the interaction effect is no longer significant. This suggests a pattern where having an easier temperament predicts fewer, but more severe depressive episodes, while having a more difficult temperament predicts greater number but less severe episodes. Furthermore, it may be that certain dimensions of temperament have differential effects on the quality of depression. These possible explanations may open more questions than they answer, and likewise, are important questions to explore further, which we have done in our exploratory analyses.

Exploratory Analyses

To further examine the pathoplasty model and to better understand the interaction between risk and temperament on the quality of MDEs we explored the associations between individual dimensions of temperament and qualitative markers of major depression. For the overall sample, difficulty adapting to new situations and irregular sleeping and eating patterns predicted greater frequency of MDEs. This may suggest that as life presents stressors individuals who can adapt quicker will not fall into depression, while those who struggle to adapt may become overwhelmed and more frequently become depressed. In addition, poor sleep patterns are diagnostic of depression, but moreover, are evidenced by disruptions in biological mechanisms that regulate sleep, primarily the suprachiasmatic nucleus (SCN) which regulates the neurohormone melatonin. Significant evidence links the dysregulation of melatonin release and reuptake with depression (see Sriniviasan et al., 2007 for review). In addition, changes in

the hypothalamic-pituitary-adrenal axis (HPA) which regulates cortisol secretion and corticotrophin releasing hormone (Stetler & Miller, 2005), reduction in slow wave sleep, and decreased latency of rapid eye movement (REM) sleep are commonly found in people with depression (Sriniviasan et al., 2007). A predisposition to arhythmicity as assessed by the DOTS may reflect a vulnerability to changes in biological mechanisms affecting the sleep-wake cycle putting individuals at increased risk for recurrent depressive episodes.

Next, we found that individuals who are more easily distracted with shorter attention spans have shorter duration of MDEs. At first this appears a curious finding since high inattention is loaded towards difficult temperament and there exists high comorbidity between attention-related disorders such as adult ADHD and major depression (Klassen, Katzman, & Chokka, 2010). We would expect inattention to predict longer duration of MDEs. Furthermore, within the current study population pre-pubertal anxiety disorders (also related to attention deficits) were a precursor to later development of major depression especially among high-risk offspring (Weisman et al., 2006). However, there may be alternative explanations for this finding as well. First, the tendency to be easily distracted may actually reflect a protective function of distraction and the deleterious effects of rumination. Evidence supporting *response styles theory* (Nolen-Hoeksema, 1991) has demonstrated that rumination, which involves repetitively and passively focusing on distressing symptoms and their causes and consequences, exacerbates and prolongs depressed mood states (Kuehner & Weber, 1999; Nolen-Hoeksema, Morrow, & Fredrickson, 1993; Nolen-Hoeksema, Parker, & Larson, 1994), while distraction activities in response to negative mood state has been shown to reduce severity and duration of depressed mood (Joorman & Siemer, 2004; Trask & Sigmon, 1999). While our study does not examine rumination per se, it does assess the temperamental predisposition towards distraction

and inattention, and response styles theory could explain why greater distractibility in our sample is associated with shorter and less severe depressive episodes.

Second, research on the neurobiology of temperament has discerned three separate attentional networks including the alerting, orienting, and executive attention which correspond to different neuroanatomical structures and neurotransmitters (Posner & Petersen, 1990; Posner & Rothbart, 2007). These networks have unique effects on various components of attention-related, anxiety, and depressive disorders. For example, ADHD is related to deficits in alerting and executive attention, anxiety disorders are related to deficits in orienting attention, and depression to deficits in executive attention. The current study does not examine these attentional networks separately and in fact includes attention and distractibility within the same dimension when it appears they are themselves distinct behaviors. It is possible that the protective function of distraction is more dominant in this sample than the negative impact of inattention. Finally, clinical evidence-based treatments for depression and other major mental disorders involve distraction, cognitive-behavioral, and behavioral-activation skills (DBT: Linehan, 1993; CBT: Beck 1995; IPT: Weissman, Markowitz, & Klerman, 2000) which may essentially be targeting and seeking to promote the development of this partly inborn predisposition.

Exploratory analyses also revealed that severity of major depressive episodes was related to activity during sleep and inattention/distractibility; more active individuals who are more easily distracted reported less severe depressive episodes. Again, we see an inverse relationship between attention and a negative qualitative marker of depression and where a similar process of distraction or shifting attention away from a negative mood state may be serving a protection function by reducing the severity of a depressive episode.

These results differed slightly for high risk compared to low risk offspring. Given the interaction between risk status and difficult temperament in predicting severity of MDEs, the most salient point to discuss is how different dimensions of temperament relate to severity across risk group. Among high-risk offspring activity marginally predicted severity of MDEs, while among low-risk offspring attention/distractibility significantly predicted severity, and rhythmicity marginally predicted severity.

Together, the exploratory findings provide at least partial support of the pathoplasty model of the temperament – psychopathology link and indicate that individual dimensions of temperament have unique effects on distinct qualitative markers of depression. Overall difficult temperament is associated with greater number of lifetime depressive episodes, more specifically, dimensions of adaptability and rhythmicity were associated with increased frequency. In addition, attention/distractibility was associated with shorter duration and decreased severity of depressive episodes, while activity during sleep was also associated with decreased severity. These important findings suggest that 1) not all depressive episodes are created equal, and 2) variations in the phenomenology of depression may reflect specific temperamental profiles. That is to say, depression may be more idiographic than otherwise.

The implications of these results are two-fold. First, just as not all depressions are created equally, not all depressions can be treated equally. A person with a predisposition towards irritability and general activity may require cognitive restructuring of “hot cognitions” or distress tolerance skills, while a ruminative individual may do better by learning distraction and behavioral activation techniques. Second, the results speak to a broader discussion about dimensional versus categorical models of psychopathology. If certain dimensions of temperament (and likewise, the personality literature has much to add) predict certain

characteristics features of depression than it behooves us as clinicians to pay more close attention to dimensional aspects of temperament/ personality rather than diagnostic categories of mental disorders. Interestingly, psychiatry and clinical neuroscience may be indirect proponents of dimensional models even as they work explicitly within the medical model. Psychotropic medication is largely proscribed based on side effect profiles, which serve as clinical indicators for different types of depression. For example, given that all SSRI's function by reducing the reuptake of serotonin, the anxious-depressed person may be prescribed Paxil because of its sedating properties, while the lethargic-depressed person may be prescribed Lexapro because of its activating properties.

Limitations

The current study has notable strengths and weakness. It is the longest reported follow-up of high-risk offspring and comparison offspring that we are aware of and the attrition rate was exceptionally low over the 20 years. However, there are important limitations to consider. First, temperament data is all self-report. While temperament was assessed as early as possible (initial interview), it is still dependent upon recall of behavioral style as a child and thus subject to various biases including memory distortion, current or previous psychopathology, and subclinical symptoms. These reflect potential state-dependent factors (vs. trait – temperament). Observational studies are frequently used to control for such limitations. However, the stability of temperament is widely accepted, and has been shown even within the current study sample (Mufson, Fendrich, & Warner, 1990), and thus we can assume with relative confidence that our results reflect trait-dependent rather than state-dependent processes.

Second, the external validity (generalizability) is limited. The original proband sample of depressed parents was recruited from a treatment center and all met criteria for moderate to

severe major depressive disorder. Therefore, we cannot generalize to a community sample of people with milder forms of depression who are not receiving treatment. However, given we are examining the impact of biological predisposition to depression and that temperament has a biological component, using a more severely depressed sample is arguably a more desirable choice.

Third, the sample was relatively small, with a large age distribution, and entirely homogeneous. Small sample size reduced power and limited our ability to conduct more detailed analyses by gender or other demographic variables. Relatedly, the sample was entirely Caucasian and largely Roman Catholic. While this provides a more genetically uniform sample, it precludes the examination of racial or ethnic variations in depression and temperament. In addition, the age range was large and while we adjusted for baseline age in our analyses, a larger more tight-knit age cohort may have allowed us to draw more firm conclusions about developmental processes related to temperament and depression.

Finally, the study was conducted for epidemiological purposes, rather than clinical, and there are inherent limitations in using epidemiological data for clinical studies. The interviewers were not seasoned clinicians and the foci of the study were particularly broad rather than focused on specific clinical phenomena or processes. Given these limitations, the current study provides important evidence showing that dimensions of temperament affect not only the risk for, but the presentation of major depression.

Future Directions

As diagnostic classification shifts towards a more dimensional approach, it is important to continue exploring conceptual models linking temperament/personality with psychopathology. The current study provided evidence for the vulnerability and pathoplasty models. Yet, these

models are not mutually exclusive and perhaps a more thorough integrative perspective will emerge with continued research. It may be that different models are more relevant at different developmental stages, that certain models better account for specific disorders, or that a combination of models is most appropriate. For example, in our study parental depression and offspring temperament increase the chances of later development of major depression (vulnerability) but difficult temperament then affects the quality of major depression (pathoplasty).

Research examining mediators and moderators of these relationships will also be important towards this end. For example, psychosocial factors such as social supports and peer influences may interact with temperament and depression. Likewise, intrapersonal factors such emotion regulation, coping skills, and response styles are also important to consider. Response styles theory (Nolen-Hoeksema, 1991), for example, is strongly linked to depression. It would be interesting to explore how response styles theory interacts with temperament to predict risk for depression and quality of depressive episodes. Likewise, coping skills or the ability regulate negative affect may mediate the relationship between temperament and depression; and yet emotion regulation and temperament are both at least partly biologically determined so teasing apart these effects is crucial.

Future research must also recognize that individuals who appear well-adjusted or "easy-going" may be at equal or even greater risk for severe depression. While having a biological predisposition towards depression may increase risk for lifetime incidence, environmental factors may have more powerful effects on those who appear well-adjusted. One possibility is to reexamine the "goodness of fit" theory posited by Thomas and Chess in their seminal New York Longitudinal Study. This model proposes that different temperamental profiles predict optimal

adjustment when ensconced in the appropriate parenting environment. That is, a child with difficult temperament may require more firm limit-setting, while a more passive child may respond best to less intensive parenting style. Likewise, the relationship between temperament and parenting is transactional and understanding how temperament elicits certain parenting styles is important.

Genetic research may offer insight into the complicated relationship between temperament and depression. As discussed, candidate genes can produce vulnerability to depression and certain temperamental traits. In addition, gene x environment interactions have been found whereby genetic makeup predicts depression in response to environmental stressors. Further research on candidate genes may elucidate differential associations between genes that put individuals at risk for incidence of depression, and genes that exacerbate the disorder when already present. Furthermore, different dimensions of temperament may be related to different genetic vulnerabilities. Exploring these considerations is highly important and possible as technological advances continue to emerge. Relatedly, research across racial and ethnic groups is important and could help explain unique pathways and presentations of depression and temperament among different demographic groups.

Conclusion

The current study examined the relationships between parental depression, offspring depression, and offspring temperament. It is one of the longest multigenerational follow-up studies with high and low-risk comparison groups to our knowledge and participation was exceptionally high over the 20-year study period. Overall, we provide strong evidence that parental depression predicts offspring depression and offspring difficult temperament while adjusting for family effect. In addition, offspring difficult temperament predicts lifetime

depression regardless of risk status. Perhaps the most important finding is that the relationship between temperament and depression is far more nuanced than simply ‘does difficult temperament predict lifetime depression?’ As evidenced in the current study, certain dimensions predict more frequent depressive episodes, while other dimensions predict duration or severity of episodes. Moreover, these associations vary among offspring with or without a family loading for depression. This suggests that variations in the qualitative indicators of depression may be more idiographic than otherwise. Continued research towards an integrative model of temperament-psychopathology link will help elucidate the composition of mental illness and its various incarnations.

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APPENDIX A: Measures

(1) Dimensions of Temperament Scale (DOTS; Lerner et al. 1982)

Form DJ; Page 2

		TRUE	FALSE	
ADAP 19.	In meeting a new person I tend to move towards him or her.	1	2	(50)
REAC 20.	When I react to something, my reaction is intense.	1	2	(51)
ATT 21.	If stopped from doing something, I will always go back to it.	1	2	(52)
REAC 22.	I never seem to slow down.	1	2	(53)
ADAP 23.	It takes me no time at all to get used to new people.	1	2	(54)
ATT 24.	If watching something, I will keep at it for a long period.	1	2	(55)
ACT 25.	I move a great deal in my sleep.	1	2	(56)
RHY 26.	I seem to get sleepy just about the same time every night.	1	2	(57)
ADAP 27.	I move towards new situations.	1	2	(58)
RHY 28.	When I am away from home I still wake up at the same time each morning.	1	2	(59)
RHY 29.	I eat about the same amount at breakfast from day to day.	1	2	(60)
ACT 30.	I move a lot in bed.	1	2	(61)
ADAP 31.	*It takes me a long time to get used to new people.	1	2	(62)
RHY 32.	I eat about the same amount at supper from day to day.	1	2	(63)
ACT 33.	*I don't move around much at all in my sleep.	1	2	(64)
RHY 34.	My appetite seems to stay the same day after day.	1	2	(65)

(2) Best Estimate Forms

Waves 1 & 2

DSM-III RATINGS BEST ESTIMATE SUMMARY OF COURSE

FAMILY (1-5)	PERSON INTERVIEWED (6-9)	PERSON DESCRIBED (10-13)	RATER (14-15)	MONTH (16-17)	YEAR (18-19)	AGE AT INTERVIEW (20-21)
41373	1111	0023	DG	01	84	20

	No. Epis	#1 Age Yrs	#1 Wks Dur.	#1 Lev	#2 Age Yrs	#2 Wks Dur.	#2 Lev	#3 Age Yrs	#3 Wks Dur.	#3 Lev	#4 Age Yrs	#4 Wks Dur.	#4 Lev	
Major Depression	3	16	0805		19	0124		20	0144					(22-46)
Minor Depression														(47-71)
												XXXXX6004		(72-80)
														(DUP 1-13)
Multiple Minor														(14-25)
Dysthymia														(26-37)
Mania	1	18	0204											(38-62)
Hypomania														(63-75)
												X6005		(76-80)
														(DUP 1-13)
Hypomania (Cont.)														(14-25)
Multiple Hypomania	35	18	0306											(26-37)
Cyclothymia														(38-49)
Psychotic Features														(50-74)
												XX6006		(75-80)
														(DUP 1-13)
ADD		10	1562											(14-25)
Conduct Disorder	1	17	0724											(26-38)
Separation Anxiety														(39-63)
Panic	1	20	0012											(64-76)
												6007		(77-80)
														(DUP 1-13)
Panic (Cont.)														(14-25)
Agoraphobia														(26-50)
Social Phobia														(51-63)

Level of Certainty: Possible = 2; Probable = 3; Definite = 4; Definite Most Severe = 5

Wave 3

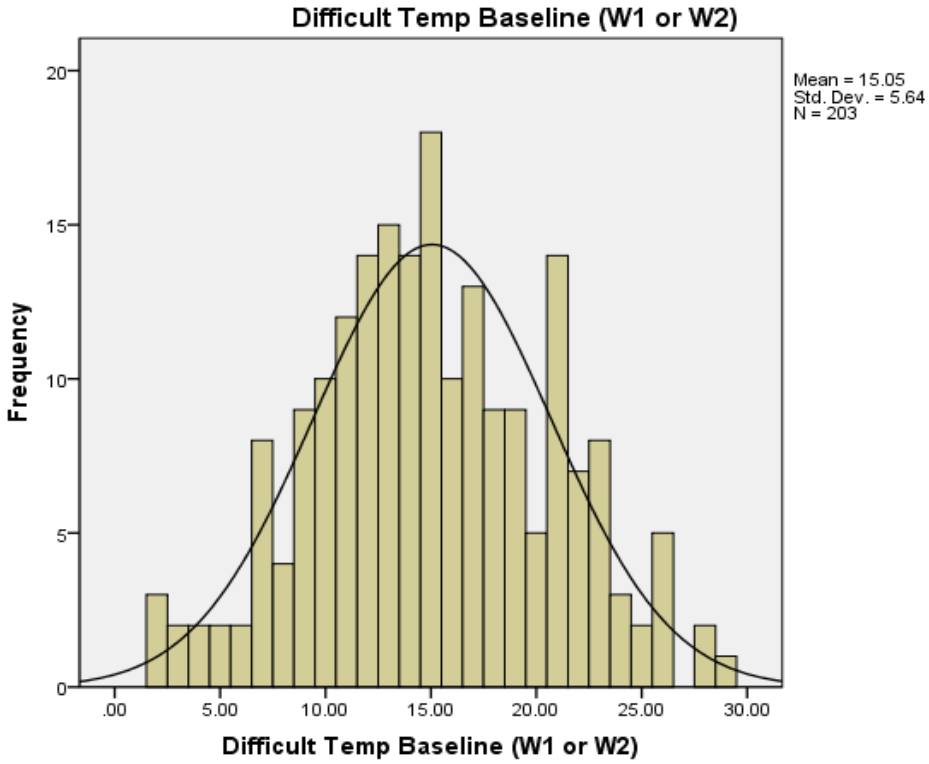
Form: DX

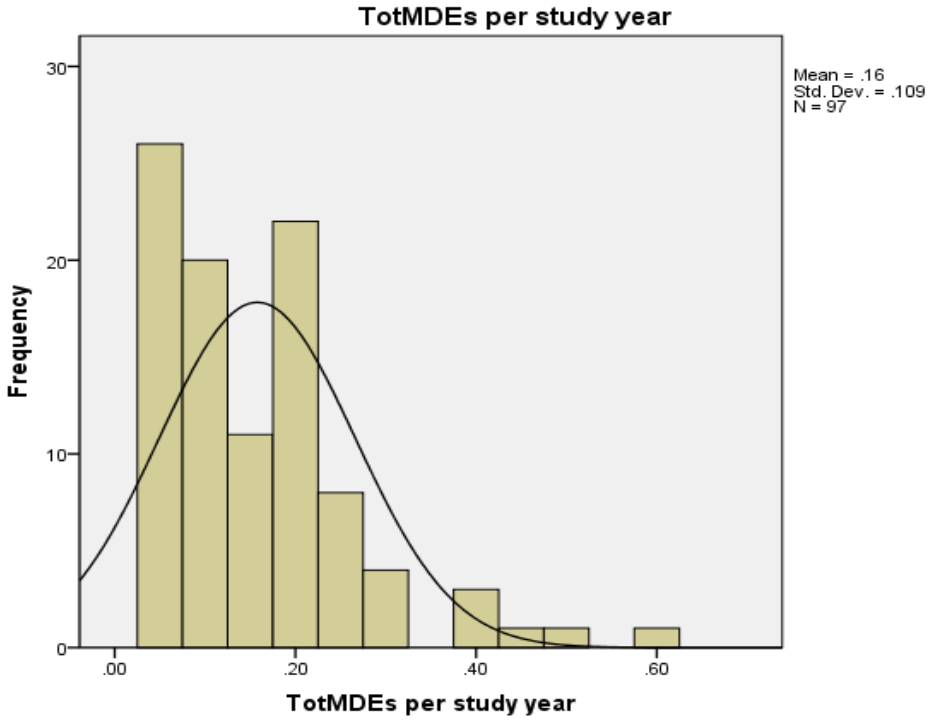
BEST ESTIMATE FORM

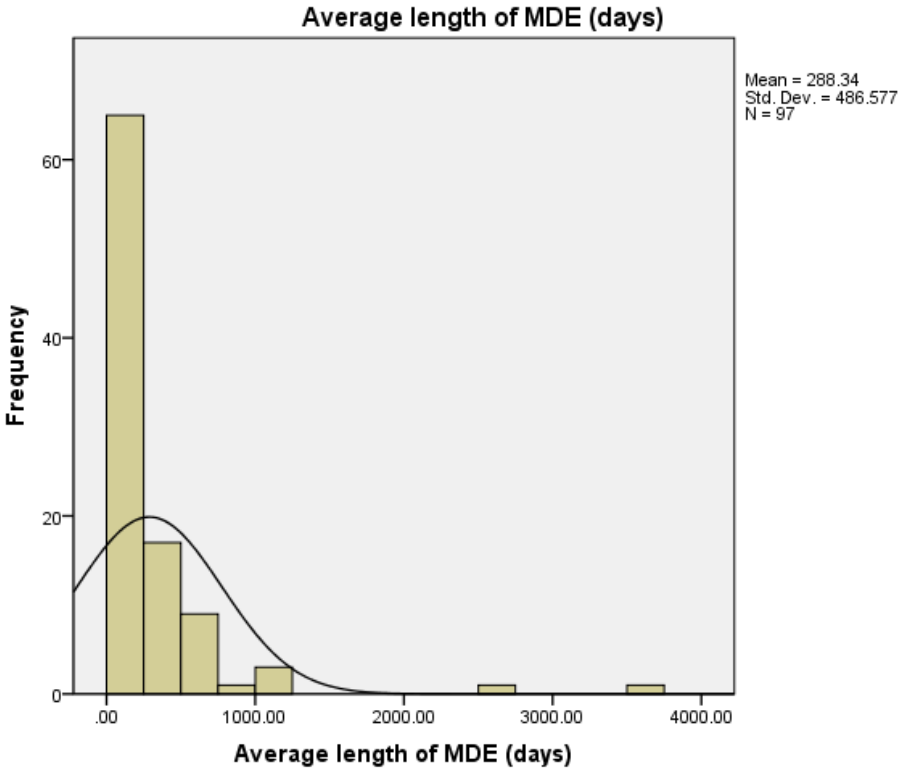
REVIEWER ID DC **SUBJECT ID** _

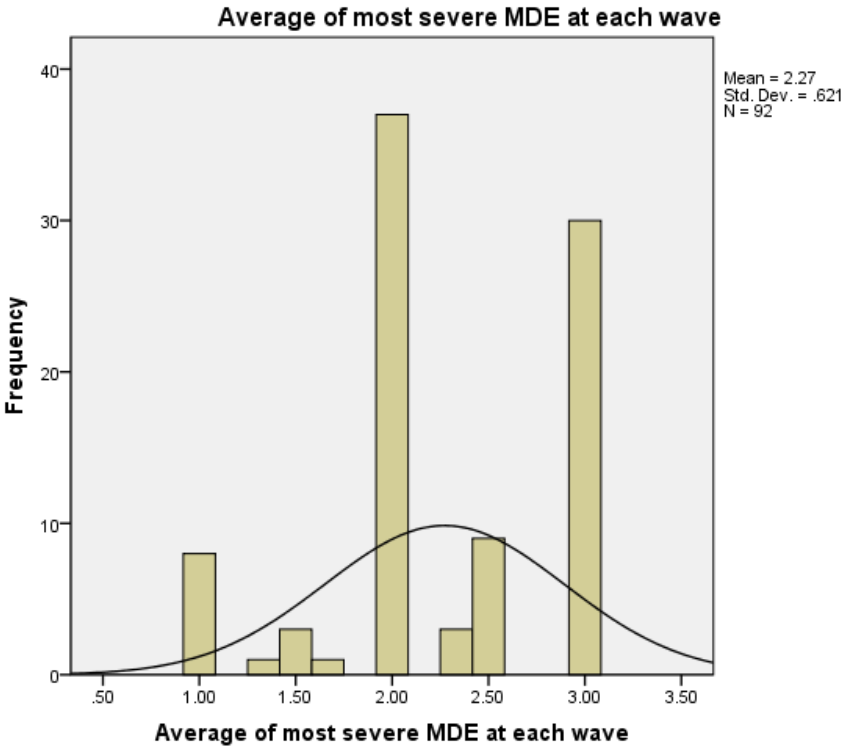
	Code of DSM-III-R Diagnosis	Diagnosis Name	Level of Certainty	Level of Symptom Severity	Level of Impairment	Month/Year Episode Onset	Duration of Episode	Other Features	Consensus Difficulty
	Use DSM-III-R 5-digit codes	Use DSM-III-R labels	1 = possible 2 = probable 3 = definite	1 = mild 2 = moderate 3 = severe 9 = unknown	0 = none 1 = mild 2 = moderate 3 = severe 9 = unknown	96 = Adolescence 97 = Childhood 98 = Adulthood 99 = Unknown	Letter codes: D = days W = weeks M = months Y = years	X = NA/NI 0 = none 1 = present atyp org	0 = Not Co 1 2 3 4
1	300.21	Mear Panic Attacks	1	1	1	03154	Y 05	XX	0
2	312.90	Conduct Disorder Unwith. Type	3	1	2	154	Y 11	XX	0
3	303.90	Alcohol Dependence	3	1	2	03165	Y 04	XX	0
4	304.30	Cannabis Dependence	3	1	2	03165	Y 13	XX	0
5	304.50	Hallucinogen Dependence	3	1	1	03165	M 01	XX	0
6	296.20	Major Depression Single episode	1	9	9	06186	M 29	00	0
7	296.30	Major Depression Recurrent	3	2	2	04190	W 08	00	0
8	SU2.30	Suicide attempt	2	9	9	06190	D 01	XX	0
9	____.__		___	___	___	__/__	_ __	__	___
	____.__		___	___	___	__/__	_ __	__	___

APPENDIX B: Histograms of distribution of all variables with normal curve overlayed.

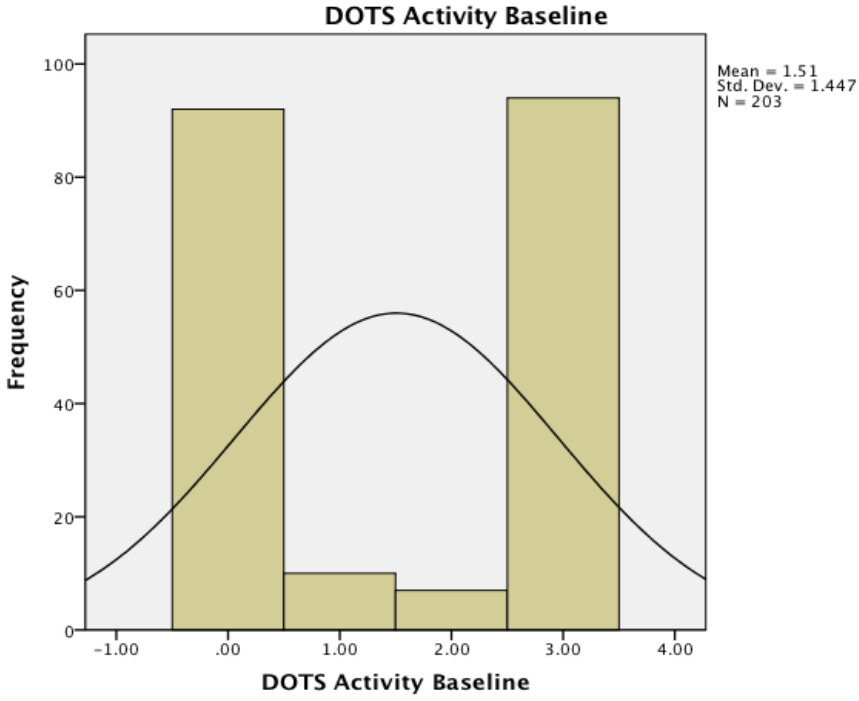





Average length of MDE (days)
Mean = 288.34
Std. Dev. = 486.577
N = 97
Frequency
60
40
20
0
.00
1000.00
2000.00
3000.00
4000.00
Average length of MDE (days)


Average of most severe MDE at each wave
Mean = 2.27
Std. Dev. = .621
N = 92
Frequency
40
30
20
10
0
.50
1.00
1.50
2.00
2.50
3.00
3.50
Average of most severe MDE at each wave


Age at Baseline Interview (W1 or W2)
Mean = 18.69
Std. Dev. = 6.556
N = 203
Frequency
0
5
10
15
0
10
20
30
40
Age at Baseline Interview (W1 or W2)


DOTS Activity Baseline
Mean = 1.51
Std. Dev. = 1.447
N = 203
Frequency
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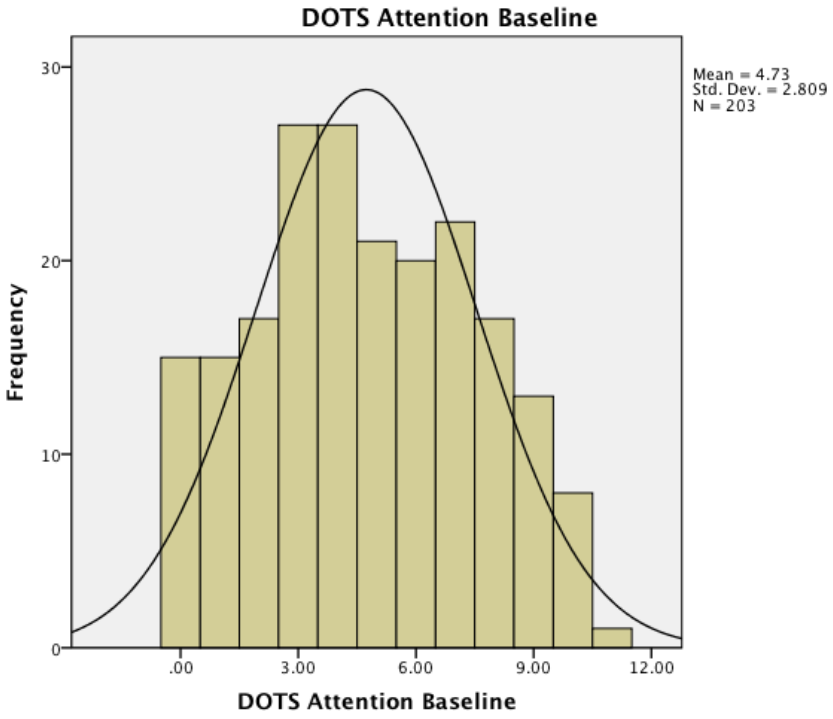
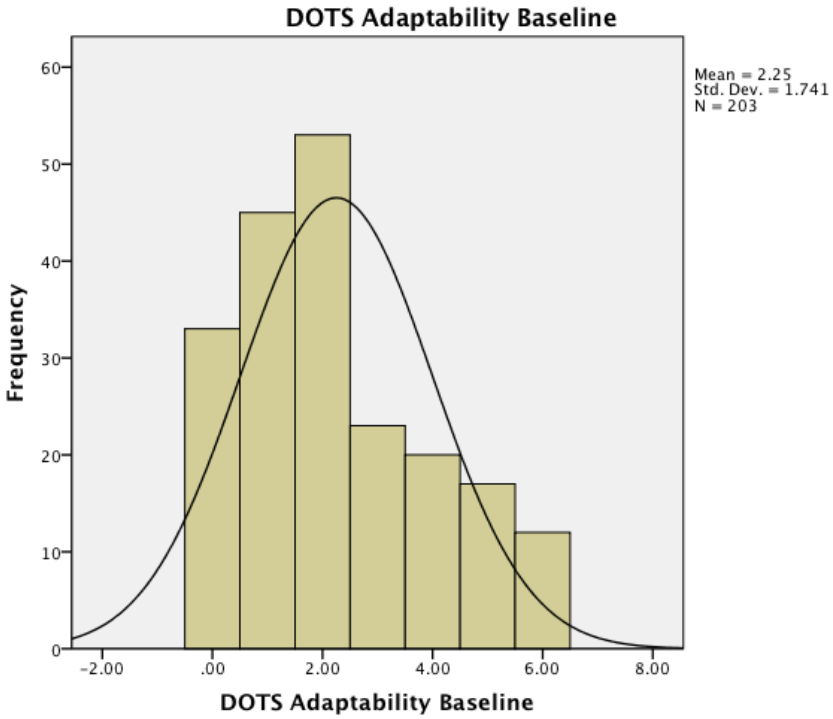
20
40
60
80
100
-1.00
.00
1.00
2.00
3.00
4.00
DOTS Activity Baseline


DOTS Attention Baseline
Mean = 4.73
Std. Dev. = 2.809
N = 203
Frequency
30
20
10
0
.00
3.00
6.00
9.00
12.00
DOTS Attention Baseline


DOTS Adaptability Baseline
Mean = 2.25
Std. Dev. = 1.741
N = 203
Frequency
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50
40
30
20
10
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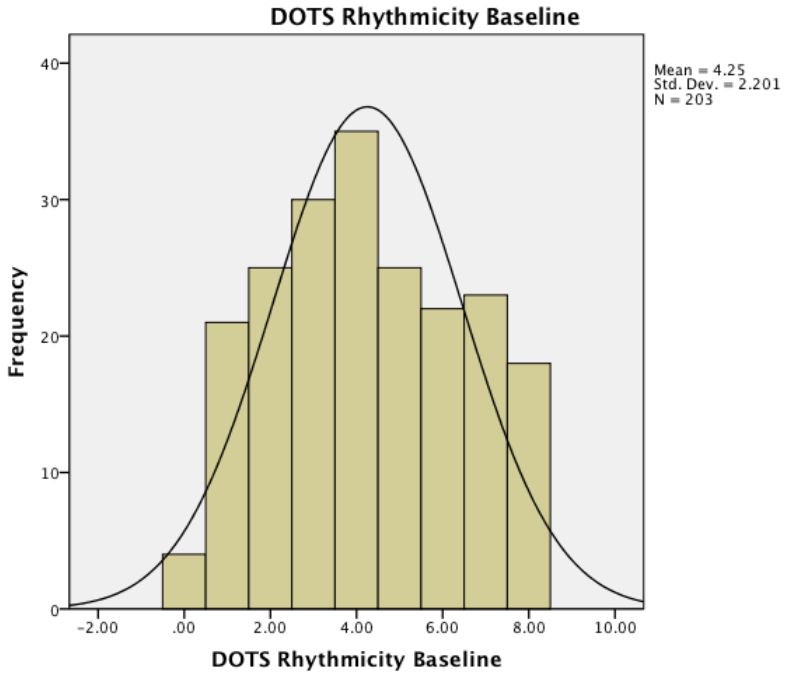
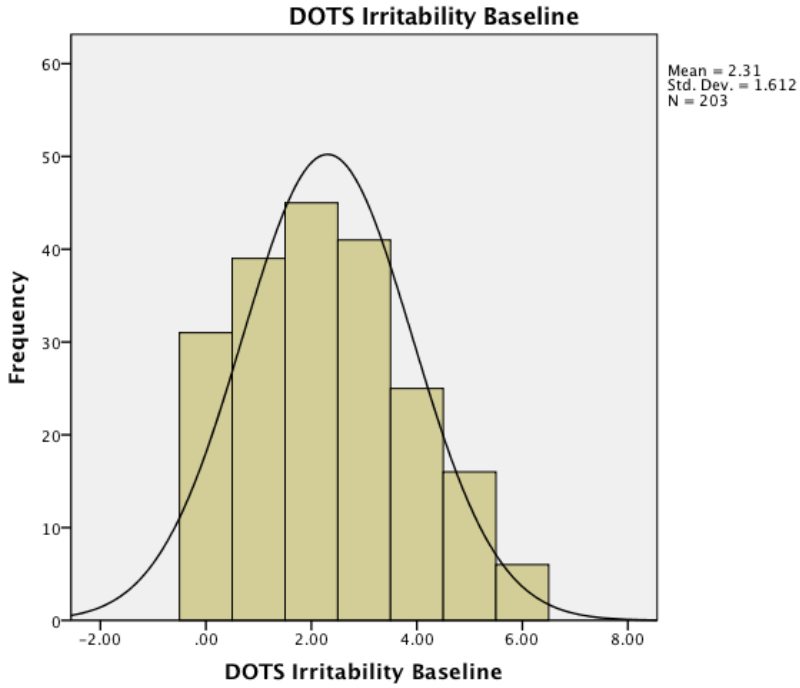
2.00
4.00
6.00
8.00
DOTS Adaptability Baseline


DOTS Rhythmicity Baseline
Mean = 4.25
Std. Dev. = 2.201
N = 203
Frequency
40
30
20
10
0
-2.00
.00
2.00
4.00
6.00
8.00
10.00
DOTS Rhythmicity Baseline


DOTS Irritability Baseline
Mean = 2.31
Std. Dev. = 1.612
N = 203
Frequency
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50
40
30
20
10
0
-2.00
.00
2.00
4.00
6.00
8.00
DOTS Irritability Baseline