Temperament, Personality and the Development of Brain Networks

Mary K. Rothbart\*, Michael I. Posner\* & Brad E. Sheese^

\* Dept of Psychology University of Oregon

^ Dept of Psycholgy Illinois Weleyan University

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Temperament and personality are distinct but interrelated domains in the study of individual differences. The study of temperament in infancy and childhood provides the necessary foundation for understanding individual differences in social and personality development. Not all dimensions of temperament are observable in the newborn’s behavior; temperament itself develops and is influenced by the child’s experience. Temperament is linked to human biology throughout the lifespan, and to the study of individual differences in nonhuman animals. Indeed, since ancient times, temperament concepts have related individual differences in behavior to the constitution of the individual as it was understood at the time. Improvements in our understanding of genes and brain networks related to thought, emotion, and action now provide an opportunity to better integrate psychological temperament analysis with neuroscientific and molecular approaches to brain development.

We have defined temperament as constitutionally based individual differences in emotional, motor, and attentional reactivity and self-regulation, showing consistency across situations and relative stability over time (Derryberry & Rothbart, 1997; Rothbart & Derryberry, 1981). The term 'constitutional' refers to the links between temperament and biology. 'Reactivity' refers to the latency, rise time, intensity and duration of the person's responsiveness to stimulation. 'Self-regulation' includes the processes that serve to modulate reactivity, including approach, withdrawal, inhibition, self-soothing, orienting and executive or effortful attention. These definitions were designed to apply to multiple levels of analysis as well as to provide a basis for the development of personality.

We do not expect that individual differences and adaptations will remain stable across life. Rather the child’s life experiences and adaptations to society will affect temperament and its expression, just as the child’s experiences and adaptations will be shaped by temperament. It is important to recognize that temperament does not refer to just a single system, but to multiple systems that inhibit or facilitate each other’s expression (Rothbart & Sheese, 2007). Consider, for example, how fear can inhibit approach.

Is it possible to differentiate between temperament and personality? We believe that it is. Throughout life, reactivity and self-regulation can be observed and studied. By assessing the reactivity of the emotions, motor activation and attentional orienting along with the efficiency of executive attention, we able to study the origins of personality. It is possible to follow sensitivity to fear, anger, reward, punishment and efficiency of alerting, orienting and executive attention across the lifespan, and relate these variables to personality and neural networks. Temperament also offers a basis for studying the development of behavior problems in children and psychopathologies of stress and attention in adults (Rothbart, 2011; Zentner & Shiner, 2012).

In recent personality research there has been a particular focus on the Big Five or Five-Factor models of trait personality. These models were constructed through multivariate analyses of self-descriptive adjectives (Digman & Inouye, 1986) and based on the premise that all significant variations in personality are represented in language. These broad trait models of personality are important and they are related in interesting ways to temperament (Evans & Rothbart, 2007; McCrae et al., 2000), but they are incomplete. Variables with labels like Conscientiousness and Neuroticism, for example, cannot describe the infant; nor can they support the study of the person’s complex adaptations during development. However, there are approaches to personality psychology with close links to temperament and the nervous system. In the first section of this review, we discuss psychobiological traditions beginning with Pavlov, Eysenck, and Gray. We also provide a brief history of temperament concepts and research, considering influential studies of temperament in childhood, their strengths and limitations. We then consider the biology of temperament in genes and brain networks, the major focus of this chapter. Finally, we conclude with a brief review of recent contributions and questions for the future.

# Historical Perspectives

Temperament has been recognized since ancient times. In Western thought, it was described in the fourfold typology of Greco-Roman physicians, who linked temperamental characteristics to Hippocrates' model of the humoral constitution of the body (Diamond, 1974). In the ancient typology, the melancholic person, quiet and moody, was seen as having a predominance of black bile; the choleric as touchy, aggressive and active, with a predominance of yellow bile; the sanguine person as sociable and easygoing, with a predominance of blood, and the phlegmatic person, calm and even-tempered, with a predominance of phlegm. The typology was related to psychopathology as in links between melancholia and depression and the choleric temperament and aggression.

Use of the fourfold typology persisted throughout the Middle Ages and the Renaissance, and was found in the writings of Kant. More contemporary researchers have also tied their findings to the typology.

In modern times, traditions of research on temperament in adults have developed in both Eastern Europe and the West. The Eastern European tradition had its roots in Pavlov’s (1935) laboratory, in the study of temperamental differences in dogs. In Pavlov’s studies of conditioning, laboratory dogs were observed over time in a variety of experimental settings. Consistent temperamental differences among the dogs were observed, which Pavlov linked to qualities of the central nervous system as posited from the conditioning research. Pavlov proposed that dogs who could continue to increase the strength of their conditioned response under high intensity or prolonged exposure to stimulation possessed “strong” nervous systems; those who easily lost it had “weak” nervous systems.

Later research by Nebylitsyn & Gray (1972), using laboratory measures and drug studies of humans, indicated that individuals with weak nervous systems also showed lower sensory thresholds than those with strong nervous systems. Problems developed for the Soviet tradition, however, when the nervous system properties they thought were general proved to be highly dependent on the specific stimuli used and the specific responses measured in the laboratory (Strelau, 1987).

In contrast to Eastern European laboratory research, early studies of temperament in the West focused on identifying its structure through analysis of questionnaire items. For example, Heymans and Wiersma (1906) asked 3,000 physicians to observe a family (parents and children) and to fill out a questionnaire on each family member. Three general factors of individual differences and 8 types were identified. Webb (1915) and Burt (1939) applied early forms of factor analysis to questionnaire items written to measure the individual’s emotionality, self-qualities, and intellect. Their work yielded factors of Extraversion-Introversion, Emotional Stability-Instability (later called Neuroticism by Hans Eysenck) and, in Webb’s research, a factor of volition or will, foreshadowing the later temperament variable of effortful control.

Hans Eysenck (1947) proposed a physiological basis for temperament. In an early model, he related Extraversion-Introversion to cortical excitation and inhibition, and Neuroticism to limbic system functioning. He later (1970) offered a revised model based on the ascending reticular activating system and individual differences in arousability. Gray (1978) revised Eysenck's theory by rotating the axes of Extraversion-Introversion and Neuroticism and positing individual differences in dimensions of behavioral activation and inhibition, along with tendencies toward fight and flight. Gray’s model continues to be one of the major psychobiological models of temperament, along with models put forward by Cloninger and colleagues (1993), Depue and Iacono (1989), Panksepp (1998), and Zuckerman and colleagues (1988). These models have been influential for contemporary research drawing connections to both temperament and personality.

In addition to questionnaire research, research in the West has also involved observational studies of children. Gesell’s (1928) and Shirley’s (1933) well-known longitudinal normative studies established the normal sequences of motor and mental development. However, they also noted striking temperamental variability among the children they observed (Gesell, 1928, as cited in Kessen, 1965; Shirley, 1933). Bergman and Escalona (1949) identified children who were strongly reactive to low intensities of stimulation in one or more sensory modalities, especially sight, hearing and touch, and Escalona’s (1968) concept of “effective experience” argued that simply characterizing environmental events does will not accurately portray a child’s experience of them. The social world is not the same for all children, as when a vigorous hug from a visitor brings active pleasure to some children but distress to others. Temperament in the child also tends to evoke different responses from adults and peers and is strongly linked to the child’s adaptations to the physical and social world (Rothbart, 2011).

Meanwhile in Europe, studies of temperament in infancy were underway. Beginning in 1950, Meili studied 3- to 4-month-old Swiss infants’ responses to unfamiliar stimuli and coded infants’ reactions from filmed recordings. The 3- to 4-month-old infants’ muscle tension and emotional distress to the unfamiliar objects predicted later reticence and shyness at 7 and 14 years (Meili-Dworetzki & Meili, 1972; Zentner, 2008).

Given these early advances in the study of child temperament, it is surprising that by the mid-twentieth century in the US, temperament was rarely discussed. Instead, social learning theories stressed the influence of reward and punishment in shaping individual differences in behavior, and later cognitive approaches stressed the development of children’s thinking (Rothbart, 2011). The situation was to change with the New York Longitudinal Study first published in the 1960’s, which we now describe.

## Thomas, Chess and the New York Longitudinal Study

It is difficult to overstate the influence of Thomas and Chess and their New York Longitudinal Study (NYLS; Thomas, Chess, Birch, Herzig, & Korn, 1963) on the study of child temperament. The couple, convinced of the importance of temperament in their adopted children, carried out study of a wide range of individual differences in infancy, taking advantage of parents’ observations of their children’s actions and reactions. Beginning with a sample of 22 infants who were 3–6 months of age, parents were interviewed at length about their infant's behavior in varying contexts such as feeding, the bath, and play. Every attempt was made in these interviews to get beyond general descriptions to specific behaviors.

Each infant reaction and its context was then typed on a separate sheet of paper, and Herbert Birch inductively sorted the descriptions into categories that came to represent the nine NYLS temperament dimensions (Chess & Thomas, personal communication, May 1992; Thomas et al., 1963). These were: 1) Activity level; 2) Rhythmicity (predictability of sleep, hunger, feeding, and elimination); 3) Approach/withdrawal (responses to novelty, conceptually similar to Kagan's later behaviorally inhibited and uninhibited children); 4) Adaptability (ease of modification of response in desired directions); 5) Threshold; 6) Intensity (energy level of reaction); 7) Mood (negative versus positive); 8) Distractibility; and 9) Attention span/persistence.

The observational nature of the NYLS and its multivariate approach has been extremely useful to the field, but an unfortunate aspect of their contribution is that the dimensions they identified over 50 years ago continue to be used in research and clinical work without revision, even though the need for their revision has been repeatedly demonstrated (Rothbart, 2011). In addition, Thomas and Chess’ (2007) concept of the ‘difficult’ child and their definition of temperament as style, i.e. the ‘how’ of children’s behavior (e.g. threshold, intensity, adaptability) rather than its links to specific emotions and attention, have been little changed, in spite of contradicting data.

The NYLS researchers used five of their nine temperament dimensions to categorize infants as “difficult” or “easy” (Thomas et al., 1963, 1968). Difficult children were described as withdrawing, mostly negative in mood, unadaptable, intense and irregular. Infants at the opposite pole of these dimensions were described as “easy.” A “slow-to-warm-up” child included infants who were withdrawing at first but low in the intensity of their reactions, and adaptable over time. The term “difficult” has been applied to large and confusing set of findings, and continues to be used in developmental research (Rothbart & Bates, 2006). Difficulty remains a value laden construct, often vague in its application.

## Revised Dimensions of the NYLS and Effortful Control: Rothbart’s Temperament Research

Research at Oregon started with items assessing the NYLS dimensions and other temperament dimensions identified in animal work and our own home observations and interviews, using a rational psychometric analysis of parent report questionnaires (Rothbart, 1981, 2011). We followed the lead of the NYLS in asking about concrete behaviors, and items were based on the observed relative frequency in specific situations. The dimensions that proved to be psychometrically sound were not the stylistic ones as expected; instead they measured reactivity of primary emotions, self-regulation of attention, and individual differences in activity level and soothability. The NYLS dimensions of intensity, threshold, etc. did not yield homogenous scales, but rather varied depending on the behavior system under study.

In factor analytic studies of parent-reported temperament in childhood, three to four broad factors have been frequently found (Rothbart & Bates, 2006). The first of these is Surgency or Extraversion, which includes activity level, sociability, impulsivity and enjoyment of high intensity pleasure. The second is Negative Affectivity, including fear, anger/frustration, discomfort and sadness, and the third is Effortful Control, including attentional focusing and shifting, inhibitory control, perceptual sensitivity and low intensity pleasure. Effortful Control is defined as the ability to inhibit a prepotent response and to activate a non-prepotent response. As executive attention skills develop in the second or third years of life and beyond, individuals can voluntarily deploy their attention, allowing them to regulate their more reactive tendencies (Posner & Rothbart, 2007; Rothbart & Derryberry, 1981; Ruff & Rothbart, 2001).

Research indicates some stability of individual differences in effortful control during childhood. For example, the number of seconds delayed by preschool children while waiting for rewards that are physically present predicts parents' reports of children's attentiveness and ability to concentrate as adolescents and adults ( Casey et al 2011; Mischel, Shoda and Peake 1988). A lack of self-control in pre-school and middle-childhood has also been identified as a potential marker for life-course persistent antisocial behaviour (Moffitt et al., 2011) and for the inattentive-disorganized symptoms of ADHD (Nigg, 2006).

Effortful Control positively predicts the development of prosocial behaviour and is related to low levels of behaviour problems (Eisenberg & Fabes, 1998). In research with adults, temperamental Effortful Control was found to be positively related to personality Conscientiousness, Surgency to Extraversion; Fear to Neuroticism; and Frustration/Anger to low Agreeableness. In addition, temperamental Orienting to Low Intensity Stimuli was related to the personality factor Openness to Experience (Evans & Rothbart, 2007).

## Kagan and the study of Behavioral Inhibition

As temperament research has become increasingly connected with neuroscience, the work of Kagan and his colleagues has become at least as influential as that of Thomas and Chess. Over the last few decades and beginning with doctoral research of Cynthia Garcia-Coll, Kagan and colleagues have documented the importance of individual differences in behavioral inhibition and uninhibition (later called exuberance) (Coll, Kagan, & Reznick, 1984.; Kagan & Fox, 2006). Behavioral inhibition has been defined as fearful inhibition to the unfamiliar; the reactive quality of this dimension is thus differentiated from temperament constructs that deal with effortful control.

Individual differences in fearful inhibition are predicted by infants’ distress and activity to the presentation of novel objects (Kagan & Fox, 2006). They show significant stability across childhood, and even into adolescence. Longitudinal research has reported some stability of fearful inhibition from two to eight years and from the preschool period to age eighteen. Behavioral inhibition has shown relations with specific neural networks, specific genes, and to later development of internalizing disorders such as anxiety (Fox et al., 2005; Kagan, Snidman, Zentner & Peterson, 1999).

Kagan’s influence on the field of temperament extends beyond behavioral inhibition. Kagan has been a persistent and influential critic of the questionnaire approach to assessing temperament and has advocated typological rather that continuous temperament constructs (e.g. Kagan, 1998; see discussion below). In our view, Kagan’s approach has strengths in its focus, but that focus comes at cost of a broader view of the developing individual, using a multivariate approach.

The behavioral inhibition approach also reminds us that a continuing problem in research is terminological. In the naming of constructs, different terms are used to describe very similar constructs, or one term is used to apply to quite different constructs. In this case, behavioral inhibition is very close to fear and anxiety, yet the construct is narrower than Jeffrey Gray’s Behavioral Inhibition System (BIS), which is linked to cues of punishment and non-reward as well as novelty. This is a common problem, and many of us have contributed to it.

# Contemporary Assessment of Temperament in Childhood

Current research on temperament in childhood makes use of parent report questionnaires, laboratory assessments of children's behavioural response to standardized stimuli, and observations of children's behavior in the home or school. Measures of temperament have also been related to psychophysiological measures, cognitive task peformance and measures of the developing personality. In temperament research, some researchers have advised against using parents as informants about their children's behaviour (e.g., Kagan & Fox, 2006). It has been felt that parental biases or lack of knowledge will yield measures that are invalid, with direct observation seen as a preferable method. However, considerable evidence indicates convergence between parent report and observational measures (Rothbart & Bates,2006). In addition, laboratory observations have their own limitations. For example, it is difficult to collect extensive information about children's emotionality in the laboratory when one emotional experience has carry-over effects that can influence another. Because temperament reflects dynamic interactions between affective and cognitive processes and there are limitations to both questionnaire and observational methods, multitrait multimethod approaches to temperament assessment have been advocated whenever feasible (see Rothbart, Sheese, & Conradt, 2009, for a discussion).

# Temperament and Brain Networks

The effort to understand how both emotion and attention are represented in the brain is important to our understanding of temperament. These studies often use simple stimuli to evoke emotions or cognitive tasks to examine attention, and EEG and MRI are used to provide links to brain networks. One fundamental question has been whether the primary emotions are individually separable or whether they are simply derived from broader dimensions of variability such as arousal and valence.

Recent studies employing multivoxel pattern analysis methods have begun to separate the neural activation in such primary negative emotions as disgust, fear, sadness and anger and positive ones such as pleasure and surprise. In a study using both music and film clips, Kragel and colleagues (2016) found widespread cortical and subcortical activation that differed for each of the six primary emotions. These findings were confirmed in resting state observations of similar brain networks, which were positively correlated with subjective reports of the feelings of the participants (Kragel, Knodt, Hariri & LaBar, 2016). Moreover, these correlations were stronger for non- overlapping areas of activation, suggesting the importance of unique brain areas in an emotion. While the primary emotions could be detected in the activation patterns, less ability to predict was found from classification based on valence and arousal strength, supporting the position that primary emotions are represented separately in brain structure.

The difficulty of separating the valence of emotion by MRI may be due to different emotions activating separate neurons within the same brain area. Recent work in mice has shown distinctive activation within the basolateral amygdala complex between the two valences. Within this structure, separate neurons are activated by positive reinforcement (reward) or punishment that evokes fear, with reward related to the nucleus accumbens and punishment related to the central medial amygdala (Namburi et al., 2015). Human work also reveals activation of the amygdala for both positive and negative primary emotions, with each emotion revealing a different set of connected areas in addition to the amygdala differentiation (Diano et al., 2017).

The research discussed so far mainly involves emotions that occur spontaneously or are elicited by positive or negative stimuli in humans or animal models. These emotions are part of reactive temperament. How is emotional reactivity related to more enduring tendencies toward negative affect? A recent review has outlined pathways that might relate phasic emotional activation to enduring temperamental negative affect (Shackman et al., 2016).

## Attentional Control Networks

The anterior cingulate is a very complex structure that forms an important node of the executive attention network (Posner & Rothbart, 2007). The cingulate along with the anterior insula are the two parts of the human brain containing projection cells with particularly long connections to other brain structures (Allman et al., 2010). There is evidence that more ventral parts of the ACC together with adjacent areas of the ventral midfrontal cortex provide control mechanisms related to both positive and negative affect (Bush, Lou & Posner 2000; Beckmann, Johansen-Berg, Rushworth, 2009), however, there is also some evidence of overlap of emotional and cogntive control in more dorsal areas of the cingulate (Smith et al 2009)

We have used parent-report questionnaires to assess temperament in children (Rothbart, 2011) and have linked effortful control to cognitive methods by use of the Attention Network Test (ANT; Fan et al., 2002). The ANT assesses conflict resolution by the executive attention network through use of flankers that could either be congruent or incongruent with the target. We have found that effortful control, as measured by questionnaire, correlates with the difference between congruent and incongruent flankers in the ANT (Rothbart & Rueda, 2005; Rueda,Pozuelos, & Cómbita 2015). This relates an important aspect of control as observed by parents to underlying brain networks and genes (Fan et al., 2003).

It is important to understand the mechanisms by which effortful control is exerted. Two mechanisms for the control of emotion are distraction and reappraisal (Kanske et al., 2011). Pictures were used to induce negative affect as recorded in amygdala activation. Both strategies were successful in reducing subjective emotional state ratings and lowered activity in the bilateral amygdala. However, distraction showed a stronger decrease in amygdala activity when compared with reappraisal. A follow up study (Kanske & Kotz, 2011) employed the flanker task to induce cognitive and emotional conflict. Conflict between the target and surround activated the dorsal ACC, while a combination of conflict and negative emotion activated the amygdala and the ventral ACC. These results generally support control of emotion by the ACC with different parts of this structure related to conflict resolution (more dorsal) and to emotion (more ventral), although there is also some overlap and interaction between the two (Smith et al 2009). The study also showed there was enhanced functional connectivity within the ACC and between the ACC and amygdala during emotional control.

The executive attention network has been related to a number of dopamine and serotonin genes (Posner et al., 2014) and it has been possible to determine how some of these genes influence development by examining their relation to parenting and other environmental factors as discussed in the next section.

# Genes and Gene Environment Interactions

The bulk of molecular genetics studies on temperament have examined how a small number of genetic variations (candidate genes) are related to some aspect of temperament. Before reviewing this literature, however, several limitations should be kept in mind. First, these studies usually do not employ large enough samples to detect small effects. Second, candidate gene studies usually examine only a small number of genes at a time. These issues are problematic as temperament is most likely dependent upon many genes of varying effect sizes and may involve many genes of very small effect. Third, while an individual's genes are relatively stable, their expression varies with development. Epigenetic changes refer to processes like methylation and histone modification that do not change the DNA itself, but can create lasting alterations in the expression of genes. Research suggests that “environmental” factors like toxins or psychological stress can trigger mechanisms that ultimately alter genetic expression through epigenetic processes (Meaney, 2010). There is some initial evidence that methylation of DNA may affect temperament in infancy (Fuemmeler et al., 2016). If methylation does play a role, important genetic variations might be modified and their associations obscured or enhanced through epigenetic effects. Consequently, findings that link genes and temperament may also vary across age groups and environmental conditions. Here we review a small number of candidate genes that have received substantial attention for their theoretical or empirical links to temperament. There are many additional genes that we touch on only briefly or do not cover here. We refer readers to Saudino and Wang (2012) for a comprehensive review.

## COMT

Catechol O’ Methyltransferase (COMT) refers to the gene involved in the production of the enzyme of the same name. COMT val158met (rs4680) is an example of a single nucleotide polymorphism (SNP) within the COMT gene where adenine is substituted for guanine, resulting in changes of its efficiency in degrading dopamine and other catecholamines (Lachman, Papolos et al., 1996; Lotta et al., 1995). It is believed that in adults, adenine carriers have more dopamine available in the prefrontal cortex due to less efficient dopamine degradation, and are consequently superior on tasks dependent on prefrontal cortical activation (Meyer-Lindenberg & Weinberger, 2006).

COMT val158met has been linked to executive functions, temperament and personality(Dickinson & Elvevåg, 2009; Voelker et al., 2009) including Sensation Seeking and Extraversion (see Calati et al., 2011 for a review). There have been inconsistencies in results linking COMT to cognitive functions and to date, meta-analytic results have not always supported the association (Barnett, Scoriels, & Munafò, 2008). However, the COMT literature continues to grow rapidly and more comprehensive COMT genotyping approaches may help address inconsistencies in the literature (e.g., Wacker, Mueller, Hennig, & Stemmler, 2012). In addition, evidence linking COMT to other temperament-related processes such as reward learning (Corral-Frías et al., 2016) may provide new avenues for understanding the mechanisms by which COMT might influence variability in temperament.

Another avenue for exploration is a more developmental examination of COMT. One potential reason for inconsistencies may be that the effects of COMT vary over the life course. As dopamine availability declines throughout adulthood, the association between val158met and cognitive functioning changes is also changing, with variations in val158met becoming more important over time (Nagel et al., 2008). This suggests that the relation between genotype and phenotype may be exquisitely dependent on development. In the first years of life, COMT enzymatic activity may be as much as half that of adult levels (Tunbridge et al., 2007), suggesting that dopamine may be overly abundant. Due to the inverted U-shaped relation between dopamine and cognitive functioning, it is possible that the relation between COMT val158met and cognitive functioning is reversed in childhood.

The issue of developmental processes mediating associations over time is not restricted to COMT; at a minimum, this logic can be extended to other genes related to dopamine signaling. The issue more broadly illustrates that researchers need to consider how genes are dynamically related to structural and functional characteristics of the brain over time and will need to employ methodologies adequate for addressing developmental concerns.

## DRD4

Five different types of dopamine receptors have been identified. One that has received much attention in the temperament literature is in exon 3 of the gene that codes for the Dopamine D4 receptor (DRD4). Most individuals have between 2 and 11 repeats of 48 base pairs at this location. Longer alleles (more repeats) appear to alter the D4 receptor’s ability to mediate signal transduction (Asghari et al., 1994). The 7-repeat variant in exon 3 (DRD4 7-repeat) is the primary focus here, but there are other known variations within DRD4, including SNPs outside exon 3 and variations within the repeats themselves that may also be important for dopamine signaling (Grady et al., 2003; Wang et al., 2004).

The DRD4 7-repeat has garnered widespread attention for its association with higher levels of Sensation Seeking (Benjamin et al., 1996; Ebstein et al., 1996) and Attention Deficit Hyperactivity Disorder (Swanson et al., 2000). Sensation Seeking is thought to reflect sensitivity to reward and motivation to seek out reward, to be fairly stable over time, and to contribute to adult Extraversion (Rothbart & Bates, 2006). The hyperactivity component of ADHD can be conceptualized as dysfunctionally high levels of Sensation Seeking, and consistent with this notion, a number of studies have shown links between temperament and ADHD (Nigg, 2006).

Animal research, including studies using knockout models, appears to confirm an association between DRD4 and exploratory behavior, novelty seeking, and risk taking (Bailey, Breidenthal, Jorgensen, McCracken, & Fairbanks, 2007; Grandy & Kruzich, 2004; Livak, Rodgers, & Lichter, 1995). Consistent with these studies, early studies showed some support for the idea that DRD4 played a role in temperamental surgency in infants and children. Ebstein and colleagues (1998) found that DRD4 and 5-HTTLPR interact to influence orienting to stimuli and motor organization in 2-week olds. Follow up studies with the same sample showed that DRD4 and 5-HTTLPR were associated with Negative Emotionality and Distress to Limitations (anger) at 2-months of age (Auerbach et al., 1999) and to physical activity and anger at 12-months of age (Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001). An alternative interpretation is that the DRDR 7-repeat may confer less Negative Affect or anxiety rather than greater approach. Consistent with this idea, DRD4 and a haplotype of 5-HTTLPR (including rs25531) were found to interact in predict negative affect, particularly Falling Reactivity, in infancy, such that infants with the 7-repeat allele and a highest expressing 5-HTTLPR haplotype had the highest levels of parental-reported negative affect (Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011).

As discussed previously, inconsistencies in findings between age groups may reflect predictable changes in brain structure and function during development. A potential source of variability is interactions with environmental factors. It has been proposed that DRD4 may actually confer greater susceptibility to environmental influences (Belsky, Bakermans-Kranenburg & van Ijzendoorn, 2007; Belsky et al., 2009; Sheese, Voelker, Rothbart, & Posner, 2007; Van Ijzendoorn & Bakersman-Kranenburg, 2006). If this is the case, then the role of DRD4 in predicting any given phenotype will be critically dependent on the environment in which the child develops.

Consistent with the differential susceptibility concept, low maternal sensitivity combined with the 7-repeat has been linked to increased externalizing behaviors in preschoolers (Bakermans-Kranenburg et al., 2006), and parent training has been shown to be most effective in reducing externalizing behavior in children with the 7-repeat allele (Bakermans-Kranenburg et al., 2008). A meta-analysis conducted by Bakermans-Kranenburg & van Ijzendoorn (2011) provides evidence that children with alleles associated with less efficient dopamine signaling do worse in negative environments but better in positive environments.

A DRD4 7-repeat x parenting quality interaction predicting Effortful Control in early childhood has been replicated in several samples. Smith and colleagues (2012) used behavior assessments of Effortful Control and both positive and negative parenting with 382 three-year-olds. They found that negative parenting was associated with lower Effortful Control, but only for children with the 7-repeat. However, this pattern was more consistent with a diathesis stress model of the interaction, in which the 7-repeat puts children more at risk for a negative outcome when combined with a negative environment, than a differential susceptibility model, in which the 7-repeat would also be associated with positive outcomes in more positive environments. This study is also notable in that it shows how molecular genetics studies of temperament can help more clearly delineate the contributions of environmental factors. An association between Effortful Control and positive parenting has been shown in previous studies (e.g., Kochanska, Murray, & Harlan, 2000). Smith and colleagues (2012) also found that an association between Effortful Control and positive parenting, but showed that it was no longer significant when controlling for negative parenting and the negative parenting X DRD4 interaction. In a subsequent study, Smith and colleagues (2013) showed that an association between inhibitory control and parenting was moderated by DRD4.

Beyond parenting, additional evidence that DRD4 may be linked to susceptibility to environmental factors comes from studies of preschool children. Berry and colleagues (2013) found that children who were 7-repeat carriers and also experienced fewer hours in daycare showed more attention and inhibitory control on laboratory tasks. They were also rated less inattentive and impulsive behavior in the classroom. For children without a copy of the 7-repeat, hours in daycare was unrelated to attention and self-regulation abilities.

## 5-HTTLPR

Serotonin, also known as 5-hydroxytryptamine (5HTT), is a neurotransmitter with a polymorphism in the gene that codes its transporter. Different numbers of repeats result in variations of the mechanism transporting serotonin from the synapse back into presynaptic neurons. Individuals with the 14-repeat version of 5HTTLPR are referred to as short allele carriers while individuals with 16-repeats are referred to as long allele carriers. The short version is believed to result in less protein production and less transport (Heils et al., 1996; Lesch et al., 1996). Consequently, individuals with the short version are believed to have higher concentrations of serotonin in the synapse.

The short allele of 5-HTTLPR has been studied very extensively as a contributor to major depression, mood disorders, stress reactivity and neuroticism in adults (e.g., Gotlib, Joormann, Minor, & Hallmayer, 2007; Lesch et al. 1996; Sen, Burmeister, & Ghosh, 2004). To date, however, research on 5-HTTLPR, including meta-analytic reviews, has yielded inconsistent support for an association. Notably, a study by Willis-Owen and colleagues (2005) examined two very large samples (N = 88,142, and 20,921) and failed to find any association between 5-HTTLPR and either major depression or neuroticism.

While studies with adults have focused on neuroticism and depression, studies with infants and children have generally examined 5-HTTLPR in relation to behavioral inhibition, fearfulness, and/or shyness. 5-HT receptor density has been linked to anxious temperament in rhesus monkeys (Oler et al., 2009) and has been linked to indicators of distress and negative affect in early childhood (Arbelle et al, 2003), but not consistently so (Battaglia et al., 2005; Hayden et al., 2007 Schmidt et al., 2002)

Several studies have examined 5-HTTLPR in relation to attentional bias to threat in infancy and early childhood. Attentional bias to threat is thought to reflect amygdala activity and temperamental fearfulness and anxiety (Etkin et al., 2004; Pérez-Edgar et al., 2010; Schwartz et al., 2011; see White et al., 2012 for a review). Perez-Edgar et al. (2010) found in adolescents that 5HTTLPR was associated in opposing directions with attentional bias to both angry and happy faces. Overall, the 5HTTLPR literature with children is even less tractable than the literature with adults. There have been fewer studies examining 5-HTTLPR in children and studiea have employed a great diversity of assessment methods and age-groups, making differences among findings difficult to reconcile.

Consideration of 5-HTTLPR in combination with other genes may help clarify findings. Recently, Green and colleagues (2016) found that both DRD4 and 5HTTLPR status influenced how exposure to prenatal maternal depression was associated with higher negative emotionality during the first 3 years of life. Maternal depression was associated with higher negative emotionality when children had both the S/LG allele of 5-HTTLPR and longer variants (6–8 repeats) of DRD4. While the two genes had individual effects, their analyses suggested that considering both genes in combination showed a stronger influence on the link between maternal depression and the child’s negative emotionality.

## Beyond Candidate Gene Studies

While the findings discussed above and others using the candidate gene approach are interesting and warrant further exploration, the history of studies linking temperament to candidate genes suggests caution in making conclusions from the existing literature. New methodologies may ultimately prove more reliable and informative than candidate gene studies. If nothing else, they may offer a chance to provide converging evidence. Advances in molecular biology now allow researchers to simultaneously examine a very large number of alleles. Rather than targeting a few locations within the DNA, as is common in candidate gene studies, researchers can sample from the entire genome and look for links to phenotypes in what is known as a genome wide association study (GWAS).

Although, to our knowledge, GWAS has not yet been applied to study temperament, another relatively recent approach involves the examination of whole-genome copy-number variations (CNVs) rather than SNPs. DRD4 is an example of a CNV that has been linked to temperament but would not be assessed in typical GWAS studies of SNPs. Genome wide studies of CNVs have shown promise for identifying genetic contributions to autism (Glessner et al., 2009), ADHD (Elia et al., 2012), schizophrenia (International Schizophrenia Consortium, 2009) and developmental delay (Coe et al., 2014). We anticipate that this approach may also prove useful for linking variability in genetics to variability to individual differences in temperament.

In sum, there have been tremendous advances in the study of temperament and genetics. However, results from this work has also revealed how difficult a problem this will be to solve. Converging evidence indicates that temperament traits are dependent upon variations in many genes, possibly hundreds, each with a very small contributions to phenotypic outcomes. In addition, some genes may show no direct effect on temperament by themselves but may interact with other genes to do so. These genetic effects may vary over the course of development or in response to epigenetic regulation. We do not currently have a literature that addresses the association between temperament and genetics at this level of complexity. Advances in molecular biology will help address some of the limitations of the genetics research reviewed here, but there is much to be done on the psychology side as well. Larger numbers of participants are absolutely crucial, and will be a formidable challenge for researchers using only lab-based temperament assessments. More thorough and reliable assessments of temperament phenotypes, including multi-method approaches across multiple points in time, will also substantially improve our ability to examine associations with genes across development.

# What have we learned about the development of temperament since our last review

In comparing this chapter to our previous review it is clear that research and theoretical work on temperament has continued to explore connections between temperament and its neural and genetic correlates. The current chapter highlights how temperament serves as a construct for examining individual differences across multiple levels of analysis, using methods and evidence from an array of fields. Advances in our understanding of the brain and advances in our understanding of genetics and developmental processes have deepened and expanded how we think about and study the development of temperament.

Temperament as a construct continues to gain traction as a tool for studying individual differences outside the confines of traditional temperament labs. A brief survey of this chapter’s references finds a remarkable number of references to psychiatry, psychopathology, pharmacology and neuroscience publications. The number and breadth of publications in these areas employing temperament constructs is remarkable. At one time temperament was viewed primarily as a niche area within social development. A survey of recent research suggests those days are well past us.

The breadth and volume of research on temperament that has been generated in the last decade also makes it challenging to keep abreast of developments in the field. The variety of methods and theories employed are a strength of the field, but also a liability in that there are few direct replications and it is often not clear to what extent findings generalize across samples or methodologies. Concerns about methodological heterogeneity are a common concern expressed by authors conducting meta-analyses of temperament and personality research. There are currently no signs of a narrowing of focus in temperament research. We hope that the multi-level approach we have advocated here will help organize and focus future research efforts.

# Future Directions

There are many opportunities to enlarge the study of temperament still further. For example, the study of temperament in animals has so far had too little influence on the study of human temperament. This should change as new methods such as optogenetics (Deisseroth et al, 2006), available only for studies in animals, allow researchers to control the activity of cells to make more precise tests on the causal nature of brain networks. By turning on or off cells in different brain areas it is possible to test the function of these areas in a more precise way. Emotions such as fear or anxiety are expressed in the brain in similar areas in humans and animals, allowing at least some level of understanding of humans through the study of animal models.

The future should bring improved connections between subscales of broad temperament categories, brain systems and pathologies. For example, we have already learned that fear and anger tendencies (sub-constructs of Negative Emotionality) are likely to set up different routes or trajectories for the development of behavior problems (see Rothbart, 2011; Rothbart & Bates, 2006). As we have seen, recent brain studies have increasingly indicated specific networks related to emotion. The future should bring increased relationships between more highly differentiated dimensions of temperament and the networks involved in the expression of emotion.

As temperament is increasingly linked to brain structure and function, our understanding of both temperament and neuroscience will be enriched. An important research question is how social and nonsocial temperament reactions can be differentiated at different ages. When, for example, is social fear (shyness) first differentiated from fear of objects? How does the developing concept of self affect social and nonsocial fear? Aksan and Kochanska (2004) have distinguished between the positive emotion expressed toward objects and toward people in infancy, and more differentiated measures related to surgency and affiliation will be helpful in addressing these research questions in the future. Studies of resting state MRI have allowed tracing humans brain changes all the way down to birth (Gao et al 2016). The advance of epigenetic studies (Meaney, 2010) have allowed a framework for consideration of how the environment could influence our understanding of gene expression. In summary, our understanding of temperament has progressed rapidly (Rothbart, 2011, Zentner & Shiner, 2012); making use of new methods and linking genes to environments can improve this progress further.

Temperamental variables such as self-control measured early in childhood have increasingly been found to predict adult outcomes (Moffitt et al., 2011). The ability to predict should be employed by interventions to see if manipulating the network involved in effortful control can improve both child and adult outcomes (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005; Rueda, Checa & Combita, 2012). We have distinguished between network training using cognitive tasks and state training using methods such as meditation and physical exercise (Tang & Posner, 2014). There is evidence that both kinds of training can enhance executive attention, but exactly who benefits and the brain mechanisms involved remain open.

Summary

Temperament describes individual differences that characterize children, and forms the basis for the development of personality. In this chapter we have summarized the progress being made in understanding the dimensions of variability, measuring them and connecting them to brain networks and genetic variability among children. Readers are referred to the Handbook of Temperament (Zentner & Shiner, 2012) to review associations of temperament to psychopathology, health, education, parenting, peer relations, culture, gender and personality. Temperament forms the vital link between the adult personality and the brain mechanisms that support it, and an understanding of temperament is essential to the understanding of personality and social development.

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