Behaviour Research and Therapy 119 (2019) 103410

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Toward a transdiagnostic model of common and unique processes leading to the major disorders of childhood: The REAL model of attention, responsiveness and learning

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ARTICLE INFO

Keywords:
Transdiagnostic risk
Early childhood
Attention
Responsiveness
Learning
Epigenetics

ABSTRACT

There is a growing recognition of the importance of identifying both trans-diagnostic risk factors across the major disorders that onset early in childhood, as well as precise vulnerabilities that differentiate among specific disorders. In this paper, we propose a model to explain individual differences in the development of the major forms of mental health problems that can be identified early in life through excesses and deficits in emotional attention, responsiveness and learning (i.e., the REAL model). The model leads to a number of specific hypotheses relating to trans-diagnostic (common to all disorders) and specific risk to the major mental disorders of childhood. Like earlier models of temperament, the REAL constructs are defined in terms of how the child responds to environmental conditions. Our proposal is that the development of psychopathology is in part based on how adverse environmental conditions trigger, inhibit, and interact with these specific biological vulnerabilities at sensitive periods in the developing human. To illustrate this interplay of biology and experience, we summarize key findings from the growing field of epigenetics and child mental health, arguing that epigenetic processes might mediate the relationship between environmental adversity and the major neurodevelopmental systems of REAL. Finally, we argued that the REAL model highlights important avenues for early intervention based on common and unique factors across childhood disorders.

1. A statement of the problem

The origins of many mental health disorders are identifiable early in life, and intervention programs that identify early risk and enhance environmental influences such as quality parenting are effective in significantly reducing lifetime impairments associated with these disorders (Nock, 2003). This is a major achievement of the health sciences but is offset by evidence that the most effective of these interventions (e.g., parent training for conduct problems, and cognitive-behaviour therapy (CBT) for anxiety disorders) only produce clinically significant change in around 50% of cases (Ginsburg, Becker et al., 2014; Nock, 2003). Outcomes are considerably worse for children with multiple problems, which seems to be the rule rather than the exception for children being seen in clinics for mental health problems (Weisz, 2014a; 2014b). Research into the major diagnoses of childhood, autism spectrum disorder, disruptive behaviour disorders (DBDs), ADHD and anxiety disorders, has largely ignored this co-morbidity of problems and has typically investigated these specific disorders in isolation from one another.

However, recently there has been an increasing focus on attempting to delineate both common and unique causal processes to psychopathology (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). In this paper we contribute to this emerging focus on both unique and trans-diagnostic causal processes by presenting a model of how individual differences in several critical neurodevelopmental propensities can shape mental health versus disorder across multiple domains. First, it attempts to integrate what is known about propensities to the major disorders of childhood with research on the common dimensions of temperament that are displayed in the first few years of life. From this integration, it specifies testable hypotheses for how certain temperamental propensities delineate commonalities and points of divergence in the early emergence and subsequent pathways of the most common disorders of childhood. Second, we apply the model to the growing field of epigenetics and developmental psychopathology. Biological

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https://doi.org/10.1016/j.brat.2019.103410
Received 14 November 2018; Received in revised form 6 May 2019; Accepted 24 May 2019
Available online 01 June 2019
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approaches to development and mental health have rapidly expanded in the last few decades and include approaches focussing on neural activation and structure, genetics and epigenetics, psychophysiology and neurohormonal function. Traditionally, individual differences in biological function were tested against psychiatric categories. However, the domain specific focus has argued that they should be tested against more dimensional aspects of development and developmental psychopathology (Insel et al., 2010). Thus, one criteria for the utility of a psychological framework should be its worth in being able to organise and make sense of biological findings. Thus, we apply the REAL model to epigenetics as an example of this utility.

We want to be clear from the outset that the model we are proposing is far from proven. That is, we recognize that many (if not most) of our proposals are in need of further testing. However, we feel that the model is based on a number of assumptions that do have strong support from research and can help guide additional work by specifying clear and testable hypotheses. Specifically, our model is based on the fairly well supported premise that most common mental health problems have their roots early in life (Copeland, Shanahan, Costello, & Angold, 2009). That is, the vast majority of referrals to mental health services for children are accounted for by four groups of disorders: Disruptive Behaviour Disorders (DBDs); Anxiety disorders; ADHD; Autism Spectrum Disorders (ASD) (Olfson, Blanco, Wang, Laje, & Correll, 2014). These disorders not only typically onset early in childhood, early onset of these problems (before age 10) is associated with chronically poor social adjustment and poor psychological and physical health across development (Copeland et al., 2009). For example, DBDs and anxiety disorders are the most reliable precursors of the vast majority of adult mental health problems (Copeland et al., 2009; Kim-Cohen et al., 2003). However, our model recognizes that diagnostic categories are woefully inadequate in informing us on the causal processes that lead to these problems, largely because these disorders are not discrete categories but represent behavioural manifestations of both common and unique underlying dimensions (Insel et al., 2010; Kendler, Zachar, & Craver, 2011)The common dimensions, in particular, have led to great problems in both interpreting research and informing practice because they lead to the patterns of co-occurrence or 'comorbidity' that are found in the vast majority of children with these disorders (Lilienfeld, 2003).

A second premise of our model is that the search for environmental conditions that differentiate between childhood disorders has yielded little fruit. To be clear, our contention is not that major environmental risk factors are unimportant in the etiology of the major disorders of childhood. It is just that environmental risk factors identified for various mental health disorders, as well for other problematic outcomes such as criminality and even physical health problems (e.g., child abuse, family disruption) appear to be largely non-specific rather than unique to particular types of outcomes (e.g., WHO, 2005). In contrast, variations in critical dimensions of a child's temperament, specifically, socio-emotional attention and responsiveness, have proven to account for both unique and transdiagnostic processes that are important for both prognosis and treatment (Matthys, Vanderschuren, Schutter, & Lochman, 2012; Schechter, Brennan, Cunningham, Foster, & Whitmore, 2012). To illustrate this, DBDs are commonly, but not always, associated with high emotional lability that also increases risk for developing anxiety, depression, and substance use problems (Copeland et al., 2009). Children with high emotional lability typically show 'hot-tempered' or reactive aggression that responds well to evidence-based treatments which are largely based on reductions in hostile and inconsistent parenting (Brestan & Eyberg, 1998). In contrast, children with DBDs and low emotionality (or callous-unemotional (CU) traits) have relatively higher genetic influence and respond more poorly to many types of treatment (Hawes, Price, & Dadds, 2014), although there is emerging evidence that certain types of warm and responsive parenting can both reduce the CU traits and reduce the level of DBD's displayed by youth with elevated CU traits (Wilkinson, Waller, & Viding, 2016). This example highlights the potential importance of tracking neurodevelopmental processes that can both underlie multiple disorders (e.g., high emotional lability that leads to DBD, anxiety, and depression), as well identifying different causal processes (e.g., high emotional lability related to reactive aggression vs. low emotionality leading to CU traits) that, while leading to the same diagnostic outcome (e.g., early onset DBD), can help to identify different causal processes and thus individualized treatment needs.

2. Responsiveness, emotional attention, and learning (REAL)

Conceptual Overview. Our model assumes that, from birth, the human propensity to selectively attend to, respond to, and learn from, critical "super-stimuli" forms the basis of future socio-emotional development and health. We hypothesise that individual differences and disturbances of this system of social-Responsiveness, Emotional Attention, and Learning (REAL) are the first markers of the common emerging psychopathologies in humans. The first (super-) stimuli to preferentially engage and elicit responses in the healthy newborn are the voice and face/eyes of caregivers. From this grows selective attention and responsiveness to emotional expression, scaffolding the development of empathy, social cognition, and other higher human capacities. Specifically, we hypothesise that individual differences in the neurodevelopmental systems associated with REAL interact with the quality of environment/caregiver interactions to predict emergence of the most common forms of psychopathology, as well as social adjustment and impairment more generally. It is hypothesised that developmental variations in the neurodevelopmental systems associated with

Table 1
Constructs and Hypotheses about REAL constructs identifying common and unique features of emerging developmental psychopathology.

REAL Construct	Variables and Measures	Hypotheses (+elevated, - deficit)
Attention	Preferential attention to emotional faces/eyes, human voice (orienting to stimuli; eye tracking; coding during	DBD+, Anxiety+, CU–, ASD–
- socio-emotional	mother-infant play; joint attention).	ADHD-
- non-emotional	Emergence of preference for different emotional qualities (happy versus angry)	ASD+
- repetitive patterns	General sustained attention and response inhibition to non-emotional distractor stimuli.	
	Preferential attention to repetitive patterned, non-emotional stimuli	
Responsiveness	Facial/physiological reactivity to human faces and voices;	DBD+, Anxiety+, CU–, ASD–
- socio-emotional	Emergence of differential responsiveness to emotional quality of faces and voices; Imitative preferencing;	ASD- Anxiety+
- non-emotional	Intentional communication	ASD+
- repetitive patterns	Reactivity to novel non-emotional shapes and objects	
	Reactivity to repetitive patterned, non-emotional stimuli	
Learning	Learning of preferential responding to stimuli reliably associated with human faces, voices;	DBD+, Anxiety+, CU–, ASD–
- socio-emotional	Emergence of preference for specific emotional qualities (happy versus angry)	Anxiety+
- non-emotional	Evaluative Conditioning UCS = motion	Anxiety+
- repetitive patterns	Evaluative conditioning UCS = repetitive, non-emotional patterns.	ASD+

REAL specified in Table 1 predict both common and unique processes that lead to the development of the major childhood psychiatric disorders. By mapping both the common and unique features of emerging child psychopathology, this model not only leads to testable predictions for advancing causal theory but it aids in the identification of more precise early intervention targets for children who often present with complex comorbid conditions.

We propose that an important organising construct for identifying trans-diagnostic causal pathways and treatment needs in early-onset mental health problems, is individual differences in attention to emotional stimuli, and its corollaries of socio-emotional responsiveness and learning. These are defined as follows: 1) Emotional Attention – selectively attending to socio-emotional cues produced by other people. In the case of very young children, this is best exemplified and operationalised as selective attention to the emotional state of caregivers, and can be indexed using various measures of orienting and attention; 2) Emotional Responsiveness – visceral-behavioural responding to the emotional cues of other people. Again, in infancy this first emerges as facial muscle mimicry, psychophysiological responding, reciprocated facial emotional expression, gaze following or joint attention, and intentional communication; 3) socio-emotional Learning – propensity to show learned or conditioned responses to (previously neutral) stimuli that have been paired with, or are indicative of, socio-emotional cues of other people. We propose that individual deficits and excesses in each of these specific vulnerabilities are key to understanding the development of the most common early-onset mental health disorders.

By socio-emotional stimuli we mean stimuli that are conveying or typically convey information about the emotions of other people (e.g. faces, eyes, speech, emotional sounds, scenes of love, death, aggression). It should be noted that the propensity of a child to engage in each of these components needs to be considered against the child's capacity or propensity for attention, responsiveness and learning in general, and in relation to non-emotional stimuli. While attentional control in general is a positive factor in health and development (Rothbart, 2007), we are referring in this paper to attention specifically to socio-emotional stimuli. Thus, when operationalised for clinical research, a measure of emotional attention would be operationalised relative to the child's propensity to attend to control stimuli such as patterns and moving objects. This is critical for accounting for the child's baseline ability to direct and sustain attention to any stimuli, as might be influenced by ADHD, and their preference for repetitive patterns that might reveal a propensity toward autism. Thus, our model includes non-emotional stimuli and repetitive patterns as stimuli used to compare and contrast with socio-emotional stimuli (Table 1). We now summarize the research on which these predications are based.

Empirical Support for REAL. Clear evidence supports our contention that various forms of psychopathology are associated with individual differences in selective attention to critical emotional stimuli, including computerised emotional faces, sounds and postures. These differences are most important when expressed early in development as a failure to attend to the socio-emotional cues of attachment figures. Disrupted selective attention can drive cascading errors in the development of social cognition, empathy, and conscience (Blakemore, 2008; Skuse, 2003). The human face and its emotional expressions are 'super-stimuli' (Fox & Damjanovic, 2006) that automatically set off specific neurodevelopmental systems central to human development. Stimuli involving faces and eyes are therefore widely used to investigate emotion processing. Neural and behavioural responses' to emotional faces differ between healthy people and those with various forms of psychopathology, and specific responses to particular emotions (e.g., fear versus anger versus happiness) can differentiate between various forms of psychopathology such as depression, anxiety, and DBD (Leist & Dadds, 2009). Adults with psychopathy, and youth with elevated CU traits are hypo-responsive to emotional faces, particularly those displaying fear (Marsh & Blair, 2008). Adolphs and colleagues (Adolphs et al., 2005) have shown that fear blindness associated with amygdala-damage is due to neglect of the eye region; unlike healthy people, the person with amygdala damage fails to naturally attend to the most emotionally salient aspects of the environment, in this case the eyes of other people. Automatic attention to the eyes occurs very early in healthy newborns and is involved in attachment processes and the development of many human qualities such as empathy and theory of mind (Skuse, 2003). Other common forms of psychopathology are characterised by different distortions in emotional attention and recognition; that is, autism, schizophrenia, psychopathy, depression, anxiety, obsessive-compulsive and mania/bipolar disorders, all have been linked to problems attending to and reading other people emotions (Guyer et al., 2007). Such impairments can result from neurological damage (Bornhofen & McDonald, 2008) but can also represent temperaments that are risk factors for the development of mental health problems (Marsh & Blair, 2008).

Unfortunately little is known about the early trajectories of these impairments and their relation to the early development of psychopathology. Notable exceptions to this are recent landmark studies into attention to emotional stimuli in childhood anxiety disorders, autism and CU traits. For example, Jones and Klin (2013) recently showed that children with autism show selective attention to their mother's faces/eyes up until 12 months of age at which time attention deteriorates to become a characteristic core feature of the disorder. A longitudinal study in the United Kingdom (Bedford, Pickles, Sharp, Wright, & Hill, 2014) showed that selective face tracking at 5 weeks of age negatively predicted CU traits at 2.5 years (i.e., less selective face tracking predicting higher CU traits). These studies highlight the potential of research into early pathways in REAL constructs to reveal critical impairments and timings in the origins of different pathologies that may share similar features such as lack of empathic concern to the feelings of others.

Disorders of fear and anxiety also begin early in life and are also likely to involve developmental differences in REAL constructs. While children with ASD and DBD with elevated CU traits show impairments in attention to face/eye features, those with high anxiety tend to show biased attention to eyes/faces. Rapid, unconscious capture of attention by threat stimuli, including human faces and eyes, is a feature of adults with anxiety disorders (MacLeod & Mathews, 2012). Manipulation of this attentional bias may reduce anxiety and improve coping (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). A number of recent reviews integrating attention and learning processes in the development and maintenance of anxiety and depression, indicate that variations in attention, responsiveness and learning are characteristic of anxiety problems in late childhood and youth as well (e.g., Fu & Pérez-Edgar, 2019; Lau & Waters, 2017; Platt, Waters, Schulte-Koerne, Engelmann, & Salemink, 2017; Waters & Craske, 2016). The evidence for manipulation of attention biases ameliorating anxiety is however less clear in children and youth (Cristea, Mogoaşe, David, & Cuijpers, 2015; Mogg, Waters, & Bradley, 2017), and little is known about the development of these REAL processes early in life with regards to the latter development of anxiety disorders.

Whereas these examples illustrate how deficits or excesses with socio-emotional attention can individually amplify risk for psychopathology, it is also important to consider how these REAL constructs are interdependent. For example, emotional reactivity leads to preferential attention to threat stimuli, which in turn, escalates emotionality. High levels of emotion (and attention) facilitate conditioned learning whereby unconditioned 'super'-stimuli drive (or fail to drive) aversive conditioning to common neutral stimuli. Escalating circular relationships between socio-emotional attention, responsiveness, and conditioned learning are central to the most successful and empirically-supported models of adult (MacLeod & Mathews, 2012) and youth anxiety, depression and trauma (Fu & Pérez-Edgar, 2019; Lau & Waters, 2017; Platt et al., 2017; Waters & Craske, 2016) They also feature in emerging models of aggression and antisocial behaviour, whereby healthy prosocial behaviour is seen to involve the child learning to

avoid aggression and other antisocial behaviour through aversive conditioning. As proposed by Frick, Ray, Thornton, and Kahn (2014) when a child becomes aroused by the distress of others (e.g., emotional contagion), he or she is motivated to avoid behaviours that lead to the distress in others (e.g., aggression). Further, arousal to punishment leads a child to avoid behaviours that are sanctioned by parents and others (e.g., teacher). In both cases, failure to become aroused, either to the distress in others or to cues to potential punishment, can disruptive the development of prosocial emotions (e.g., empathy and guilt) that serve to inhibit aggressive and rule-breaking behaviours. Thus, within the REAL model, aggressive antisocial behaviour represents a failure of this developmental process whereby the child fails to learn competent social cognition, empathy, and to inhibit aggressive antisocial behaviour, due to impairments in emotional attention and responsiveness and the subsequent deficits in learning that results from these impairments.

Testable Hypotheses. We propose that individual differences in the REAL constructs will account for common and unique variance in early-onset mental health problems and, as a result, identify unique and common treatment needs of these children. Table 1 shows the specific deficits (−) and excesses (+) in REAL processes (and corresponding measures) that we hypothesise are characteristic of the different forms of childhood mental health problems. Where the disorder is not listed, we propose no disturbance on that REAL process. Of note, we list DBD and CU traits separately in both Table 1 and in the text below when we are making predictions. This is despite the fact that in the most recent editions of both the Diagnostic and Statistical Manual for Mental Disorders (DSM-5; American Psychiatric Association, 2013) and the International Classification of Disease (ICD-11; World Health Organization, 2018) use CU traits to designate subtypes of either Conduct Disorder (DSM-5) or both Conduct Disorder and Oppositional Defiant Disorder (ICD-11) with the specifier “with Limited Prosocial Emotions”. However, our model makes very different predictions for how the REAL constructs will be related to these DBD, depending the presence of elevated CU traits. Thus, we separate DBD and CU traits and, when we use DBD, we are using this to designate DBD without accompanying elevated levels of CU traits.

Our specific hypotheses can be summarised as follows: (1) *Socio-emotional Attention* will be positively associated with DBD and anxiety, and negatively associated with CU traits and ASD, whereas *Non-emotional Attention* will be negatively associated with ADHD, DBD, anxiety, and ASD; (2) *Socio-Emotional Responsiveness* will be positively associated with DBD and anxiety, and negatively associated with CU traits and ASD, whereas *Non-emotional Responsiveness* will be positively associated with anxiety only; (3) *Socio-Emotional Learning* will be positively associated with DBD and anxiety, and negatively associated with CU traits and ASD, whereas *Non-emotional Learning* will be positively associated with anxiety only. To illustrate, for Socio-Emotional Attention, we propose the following pattern of functioning: DBD +, Anxiety +, CU –, ASD - . Thus, the risk for CU and ASD would not be identifiably different on this variable, since they are both expected to be related to similar deficits. However, also measuring Emotional and Non-emotional Attention will discriminate these groups, as we expect high CU children to be unaffected in this regard.

3. The REAL model and biological vulnerabilities to experience: the example of epigenetics

Many of our REAL constructs fit within many definitions of “temperament”, such as the one proposed by Derryberry and Rothbart (1997) as involving individual differences in reactivity and regulation assumed to have a constitutional basis. That is, while these constructs are defined in terms of how the child responds to environmental conditions, they are assumed to have a neurodevelopmental basis that can in part be revealed through biological studies. Thus the following REAL constructs can be seen as a set of temperamental propensities or in the case of their dysfunction, vulnerabilities that are associated with fundamental neuro-developmental processes: 1) Emotional attention - selectively attending to emotional cues produced by other people; 2) Emotional responsiveness - behavioural responses to the emotional cues of other people; 3) Learning - the propensity of the child to show conditioned responses to (previously neutral) stimuli that are paired with the emotional cues of other people. Thus, the development of psychopathology is in part based on how adverse environmental conditions trigger, inhibit, and interact with these specific biological vulnerabilities at sensitive periods in the developing human (Belsky & Pluess, 2013), and the REAL model should be able to help structure and make sense of biological studies of child development and psychopathology. As an example of this, we focus on the growing field of epigenetics and child mental health (Babenko, Kovalchuk, & Metz, 2015; Barker, Walton, & Cecil, 2018). We propose that the interplay of individual differences in REAL propensities and vulnerabilities and environmental adversity, are in part mediated by specific epigenetic regulation of the major neurodevelopmetal systems of serotonin, dopamine, oxytocin, and cortisol. That is, epigenetic regulation of these neurodevelopmental signalling systems will be predicted by the child's exposure to adversity and will in turn, predict changes in their emotional attention, responsiveness and learning that confer broad and specific risk for the common mental health problems of childhood.

These predictions are based on research showing that the functionality of genes is regulated by epigenetic mechanisms in response to environmental influences. This can alter functional gene networks to produce a range of diseases from cancer to psychiatric conditions (Meaney & Szyf, 2005a; van Ijzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). The best characterised epigenetic processes with regard to complex behavioural phenotypes is DNA methylation, by which gene transcription is altered, often ‘silenced’, when methyl molecules bind with CpG sites in the regulatory region of the gene. A CpG site ("C-phosphate-G", that is, cytosine and guanine separated by only one phosphate) is where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases. Most of the human genome contains low (below chance expectancy) frequencies of CpG sites. However, this dinucleotide can be found at close to its expected frequency in small genomic regions (200 bp to a few kb) known as CpG islands. These areas are usually ‘protected’ from methylation and are located in the proximal promoter regions of 75% of human genes (Suzuki & Bird, 2008). Methylated CpG islands are strongly and hereditably repressed; thus, DNA methylation is a reliable marker of gene inactivation that characterizes human developmental stages, cell differentiation, and multiple pathologies, cancer being the most prominent example so far (Suzuki & Bird, 2008).

Environmental adversity such as exposure to neglectful and abusive parenting can lead to methylation of genes critical for neurodevelopment (Meaney & Szyf, 2005a; van Ijzendoorn et al., 2011). In two ground-breaking studies, DNA methylation was associated with the transmission of risk for psychiatric disorders. That is, exposing adult animals to maternal separation (Franklin et al., 2010) and olfactory trauma conditioning (Dias & Ressler, 2014) was associated with aberrant neural structures and behavioural vulnerabilities in subsequent generations, who themselves had been reared normally. The mechanism of inheritance was methylation of genes via parental gametes. Thus, methylation is one important way in which non-specific environmental adversities are coded into specific and differing outcomes in mental health both for individuals and their descendants. It offers the potential for transformative progress in mental health research. Further, there is evidence that specific methylation patterns are reversible (Dulac, 2010; Meaney & Ferguson-Smith, 2010).

Research into DNA methylation and the origins of mental health disorders in childhood studies is gathering pace (Barker et al., 2018). While, the causal role of epigenetic process remains unclear, there is emerging evidence to show that environmental factors, such as diet, neurotoxic exposures and stress, influence offspring methylation and

that variability in methylation is, in turn, associated with child and adolescent psychopathology. There have now been a number of demonstrations that methylation of genes involved in major neurodevelopmental processes predict precise variations in psychiatric diagnosis in children with early-onset conduct problems, which are relevant to our REAL model. For example, methylation of specific sites on the oxytocin receptor gene (Kumsta, Hummel, Chen, & Heinrichs, 2013) is associated with lower circulating levels of oxytocin and elevated CU traits (M. R. Dadds et al., 2014). This association was recently replicated in a 13-year longitudinal study in the UK (Cecil et al., 2014). While the first study found that higher methylation of the gene was associated with the CU phenotype post-puberty, the UK study showed that high methylation was present from birth, not present in those with high anxiety and abuse histories, and was predicted by maternal psychopathology measured prenatally but not concurrently. Thus, the transmitted risk was mediated by methylation patterns in place at birth, similar to the animal studies cited above (Dias & Ressler, 2014; Franklin et al., 2010).

Higher levels of circulating OXT have been associated with a range of biological and psychological functions. Most relevant to the current discussion is that high OXT is associated with greater attention to emotional stimuli, including the emotional faces and eye regions of human faces (Guastella, Mitchell, & Dadds, 2008). The Cecil et al. findings that higher methylation of OXTR is present at birth in children who develop high CU traits (Cecil et al., 2014) are consistent with the idea that these attentional deficits lead to a reduced preference for social stimuli and lead the child to miss out on critical developmental processes underlying the emergence of empathy and social bonding (Bedford et al., 2014). Similarly, there has also been a study showing that dampening of the OXTR gene might also be present in children with autism who are also known to show reduced attention to emotional stimuli early in life (Gregory, Connelly et al., 2009).

Another example of genetic and epigenetic variations that are relevant to the REAL model are findings that the serotonin 1B receptor gene (HTR1B) is also associated with CU traits in boys (Moul, Dobson-Stone, Brennan, Hawes, & Dadds, 2015). Moul et al. (2015) replicated the association between CU traits and a single nucleotide polymorphism (SNP) in the promoter region of HTR1B of known functional relevance to gene transcription and indexed methylation levels at 30 sites surrounding the SNP, showing that they were associated with higher CU traits. This indicates a genetically-driven alteration in serotonin function in the aetiology of CU traits, and suggests two pathways to CU traits involving sequence variations and methylation of the 1B receptor gene. Similar to OXT function, serotonin levels are known to influence attention to reactivity to emotional stimuli, such as emotional human faces. Moul, Killcross and Dadds (2012) and Moul, Hawes and Dadds (2018) have presented specific models of how oxytocin and serotonin could interact to influence amygdala function involved in the propensity to attend to, respond to, and learn from emotion stimuli as a developmental precursor to disorders of low empathy, such as ASD and those involving elevated CU traits.

A third example of research on epigenetic changes relevant to the REAL model involves methylation of the glucocorticoid receptor gene *NR3C1* promoter region 1F CpG, which has been shown to influence the development of neurobehavioral vulnerability and resilience. Meaney's group (McGowan et al., 2009; Meaney & Szyf, 2005b) demonstrated that these sites are hyper-methylated as a result of early exposure to abusive/neglectful parenting, and result in low transcription of glucocorticoid receptors in the hippocampal region, in turn predicting elevated lifetime vulnerability to heightened stress-reactivity. The relationship has been replicated in young children with conduct problems, such that those with the hyper-methylation were more likely to present with concurrent anxiety (Dadds, Moul, Hawes, Mendoza Diaz, & Brennan, 2015). With regard to the REAL model, heightened stress reactivity is associated with lifetime vulnerability to anxiety problems which are well known to predict heightened attention, responsiveness, and conditionability to threat stimuli, including negative emotional faces (Cisler & Koster, 2010).

Thus, research supports the contention that characteristics that are highly predictive of prognosis, treatment response, and treatment needs in children, relate to epigenetic regulation of the major neurodevelopmental systems in conjunction with varying exposure to environmental adversity prior to and concurrent with the onset of psychopathology. Elsewhere, researchers are finding that a) similar variations in childhood mental health and socio-cognitive function are associated with changes in DNA methylation of the major neurodevelopmental genes in the first few years of life (Szyf, 2013); b) exposure to child abuse increases methylation of glucocorticoid receptor gene in adults (Perroud et al., 2011); c) early adversity predicts differing methylation patterns in adolescence (Essex et al., 2013); and d) exposure to partner violence in mothers predicts differential methylation of cortisol receptors in their offspring (Radtke et al., 2011). We recommend recent reviews for a more comprehensive survey of this research (see Babenko et al., 2015; Barker et al., 2018).

4. The REAL model and individualized treatment

To this point, we have largely focused on the implications of the REAL model for causal theory. However, we also posit that early identification of impairments in these processes could have clear and powerful implications for treatment. The best available interventions for child and adolescent mental health problems still do not work well enough. Under controlled conditions of university and teaching hospital randomised controlled trials, using participants with relatively clean profiles (that is, without major comorbidity and other complicating presentations), the best outcomes lead to only 50% of the sample having no diagnosis at the end of the treatment; this rate falls considerably when treatments are implemented in the real-world where children often present with complex patterns of comorbid disorders (Weisz, 2014a; 2014b). Thus, we propose that the vital next step in clinical research is to develop new interventions that are targeted to the child's specific temperamental vulnerabilities and address the interplay between these vulnerabilities and adverse environments during sensitive periods in the child's development.

While this may sound like wishful thinking at this point, there is some promising evidence to support the potential treatment utility of the REAL constructs. For example, with regard to DBDs, experimental manipulations of attention, whereby children with high CU traits and adults high on psychopathy are trained to increase attention to emotional cues, are reliably associated with improved recognition of emotion and learning in the presence of salient emotional stimuli (M. R. Dadds, Cauchi, Wimalaweera, Hawes, & Brennan, 2012; Newman, Curtin, Bertsch, & Baskin-Sommers, 2010). Training attention away from emotional cues reduces fear in experimental manipulations and promotes positive coping in people with high anxiety and related disorders (MacLeod & Mathews, 2012). In ASD, training attention to the eyes can improve emotion recognition (Baron-Cohen, Golan, & Ashwin, 2009). In addition to working directly with the child, the REAL model could have implications for family-based treatments as well. Research has shown that parenting interventions work quite well for young children with DBD who show high emotionality but more poorly for those with high CU traits (Hawes et al., 2014). The identification of specific impairments to reciprocated eye gaze in these children that are present early in life ((Bedford et al., 2014), that are associated with prenatal maternal risk and methylation of the oxytocin receptor gene, and that manifest as failed engagement with caregivers during discipline and love interactions (M. R. Dadds, Allen, et al., 2012; M. R. Dadds, El Masry, Wimalaweera, & Guastella, 2008), are offering new methods for fine-tuning parenting interventions for these children. For example, there is emerging evidence that certain types of warm and responsive parenting can both reduce the level of CU traits and reduce the level of DBDs in children elevated on CU traits (Wilkinson et al.,

2016).

There is similar optimism for advancing treatment of children with ASD, which heretofore has met with very limited success. Specifically, bio-behavioural interventions targeting early deficits in face-preference and eye gaze using behavioural training and oxytocin administration are showing promise in enhancing the treatment effectiveness for children with ASD (Guastella et al., 2014). Nasal spray oxytocin has only been used with those 8 years and older, long after ASD and its component social impairments develop (Jones & Klin, 2013), and there are very good reasons to believe that targeting these face preference/eye gaze competences with integrated behavioural and oxytocin interventions may have a clinically significant impact if delivered early in life. Interestingly, there is some evidence that the oxytocin receptor system may also be differently methylated in individuals with ASD (Gregory et al., 2009), although the timing and extent of this is not known.

A final example of the potential implications for treatment relates to ADHD. Research has recently confirmed that fundamental disturbances in the dopamine D4 receptor are associated with both ADHD and adverse response to stimulant medication in children with ADHD. Specifically, negative responses to stimulant medication reactions were associated with minor alleles of a common SNP variant of the DRD4 receptor gene (Levy, Wimalaweera, Moul, Brennan, & Dadds, 2013). Further, a sequence variation was associated with increased methylation levels across the promoter region of the DRD4 gene and these methylation levels were associated with the cognitive/attentional deficits that characterize ADHD (M. Dadds, Schollar-Root, Lenroot, Moul, & Hawes, 2016). Improved understanding of how early manifestations of ADHD and its concurrent features relate to predictable variations to the dopamine gene system and treatment responses would be a step forward in both understanding of the origins of this common disorder, as well as tailoring medication treatments to the individual child.

These promising findings illustrate the potential treatment implications for REAL variables; however, the vast majority of these empirical demonstrations were all conducted with samples ranging from older to children to adults. We hypothesise that effect sizes and the generalisation of change will be considerably more impressive when they are targeted at young children during critical or sensitive periods for change. However, we recognize that such treatments may require intervening prior to problems becoming severe and impairing enough to warrant a diagnosis. However, emergent psychopathology can be measured reliably and validly as early as 3 years of age (Briggs-Gowan, Godoy, Heberli, & Carter, 2016). Specifically, core features of DBDs, excessive anxiety and fear, ASD, and ADHD are all present and measurable by this age, although there are problems with both false-positives and false negatives. In terms of false-positives, there is a proportion of children that will test positive for DBDs and ADHD at age 3 but later desist (grow out of it) and not show significant problems later in childhood (Wakschlag et al., 2014). In contrast, there appears to be a problem with false negatives when attempting to prevent anxiety disorders, whereby a substantial number of children are first diagnosed with an anxiety disorder in late childhood and early adolescence. However, there is evidence to suggest that while these children with an anxiety disorder may not have had a diagnosis at earlier ages, they often have shown long-standing problems with excessive fear, shyness, and social sensitivity that is likely to be identifiable using dimensional measures (Briggs-Gowan, Godoy, Heberle, & Carter, 2016). In short, early detection and intervention for common disorders has the potential to alter adverse developmental trajectories in ways that are clinically significant for families and children, and socially and economically beneficial for communities.

5. Limitations and issues for further consideration

There are a plethora of issues our model raises, some of which we mention here. First, the operationalisation of the model is only as good as our ability to define and reliably measure these constructs. Attention, responsiveness and learning are complex and multi-faceted constructs and the measurement properties of many of the tasks used to assess attention, learning and responsiveness can be problematic especially when used with very young children. Our model is also highly dependent upon the specification of timings at which these REAL propensities can be detected experimentally, emerge in development, and scaffold other more macro-processes such as social cognition. For example, Jones and Klin (2013) recently presented data showing that in autism, attention to emotional stimuli may develop normally through the first six months but declines after that. On the other hand, Cecil et al. (2014) showed that methylation of the oxytocin receptor gene, associated with low emotional attention, low anxiety and the development of psychopathy, is present at birth. Timing may also apply at the micro level to how attention is allocated to emotional stimuli. For example there is some evidence that emotional stimuli will grab attention in the first 20–100 ms, but provoke attentional avoidance after that in highly anxious persons (Mogg, Bradley, Miles, & Dixon, 2004; Onnis, Dadds, & Bryant, 2011; see also; Le Pelley, Mitchell, Beesley, George, & Wills, 2016).

In addition, we have presented responsiveness as if it were one construct, but clearly responsiveness consists of varying and only partially convergent systems of subjective reactions, behaviour, neural activation, and psychophysiology. These may emerge at different times, and comprise different functions. We also restricted our definition of learning to the basic associative processes involving emotional attention and responsiveness relevant to the earliest years of life. Clearly, this could be expanded to include higher functions of cognition and language as they emerge later in development.

We have also said very little about how the elements of REAL relate to each other. It is clear these elements are mutually inter-dependent. They will function contingently such that responsiveness will be in part dependent upon attention, but also in causal loops such that responsiveness to emotion stimuli will then amplify attention that these stimuli attract. Similarly, learning will be dependent on attention and responsiveness, but learning will lead to an altered system of attentional processes and responsiveness. Finally, environmental influences, such as the experience of neglect, abuse and trauma, and on the other hand, exposure to high levels of parental sensitivity and emotional reciprocation will no doubt shape the emergence and development of the REAL propensities, through epigenetic processes as discussed, but also through a wealth of other mechanisms.

6. Conclusions

In summary, there is a growing recognition of the importance of identifying both trans-diagnostic risk factors across the major disorders that onset early in childhood, as well as precise vulnerabilities that differentiate among specific disorders. Research to date has largely focused on one or the other, with the vast majority of research focussing on specific vulnerabilities. Further, this work has largely focused on vulnerabilities in older children and adolescents and not within the first years of life when the child is likely to be undergoing fundamental and pervasive changes. We propose a model to explain individual differences in the development of the major forms of mental health problems that can be identified early in life through excesses and deficits in emotional attention, responsiveness and learning (i.e., the REAL model). The model leads to a number of specific hypotheses relating to trans-diagnostic (common to all disorders) and specific risk (specific to DBD, ADHD, anxiety/depression, and ASD). Like earlier models of temperament, the REAL constructs are defined in terms of how the child responds to environmental conditions. These developmental propensities or in the case of their dysfunction, vulnerabilities, are associated with fundamental neuro-developmental processes: 1) Emotional attention - selectively attending to emotional cues produced by other people; 2) Emotional responsiveness - behavioural responses to the emotional

cues of other people; 3) Learning - the propensity of the child to show conditioned responses to (previously neutral) stimuli that are paired with the emotional cues of other people. Our proposal is that the development of psychopathology is in part based on how adverse environmental conditions trigger, inhibit, and interact with these specific biological vulnerabilities at sensitive periods in the developing human. Thus, the REAL model should help structure and make sense of both psychological and biological aspects of child development and psychopathology. As an example of the latter, we focussed on the growing field of epigenetics and child mental health, arguing that epigenetic processes might mediate the relationship between environmental adversity and the major neurodevelopmental systems of REAL. Finally, we argued that the REAL model highlights important avenues for early intervention based on common and unique factors across childhood disorders. That is, the common childhood mental health disorders have several basic processes in common and as such, child mental health services and the treatments they offer, can and should be more integrated across disorders. At the same time, the REAL model provides a framework for identifying individual differences in putative fundamental processes that can be used to fine-tune interventions according to specific impairments, rather than based on broad diagnostic categories.

Conflicts of interest

The authors have no conflicts of interest to report.

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