J Abnorm Child Psychol
DOI 10.1007/s10802-015-0024-9

Multi-Level Models of Internalizing Disorders and Translational Developmental Science: Seeking Etiological Insights that can Inform Early Intervention Strategies

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Abstract This commentary discusses the articles in this special section with an emphasis on the specific utility of multivariate, multi-level models in developmental psychopathology for ultimately contributing to both etiologic insights and translational advances. These issues are considered not only in terms of the specific papers, but also within a larger set of questions regarding the opportunities (and challenges) currently facing the field. We describe why we believe this an exciting time for integrative team-science approaches to tackle these challenges—a time that holds great promise for rapid advances in integrative developmental science that includes a biological level of mechanistic understanding. In order to facilitate this, we outline a range of approaches within both translational neuroscience and translational developmental science that can be used as frameworks for understanding how such research can provide etiologic insights regarding real-world targets at the level of social, behavioral, and affective processes that can be modified during key developmental windows of opportunity. We conclude that a "construct validity" framework, where biological data form a critical, but not privileged, component of key etiological mechanisms, combined with a developmental perspective on key period of sensitivity to intervention effects, is most likely to provide significant translational outcomes.

Keywords Developmental psychopathology · Translational neuroscience · Translational developmental science · Multi-level models · Internalizing disorders

The articles in this special section present a range of intriguing new findings regarding the developmental psychopathology of internalizing disorders. They exemplify a number of important new directions for studies in this area, including the interaction between multiple risk factors (Guyer et al., Hastings et al., Nederhof et al.) and the critical role of the parenting environment (Guyer et al., Hastings et al., Meyer et al.). All of the studies are longitudinal in nature and include multiple levels of measures and analysis, including biological measures. These biological measures were utilized either as outcomes (Guyer et al., Meyer et al.), predictors of internalizing phenomena (Giletta et al., Nederhof et al.,), or moderators of the relationships between psychosocial predictors and internalizing (Hastings et al.).

Given the emphasis in the special section on these multi-level models, the question we would like to address within this commentary is: What is the specific utility of these kinds of multivariate, multi-level models in developmental psychopathology, and most importantly how might these types of investigative approaches ultimately contribute to translational advances that make a real difference in the lives of children and adolescents vulnerable to internalizing mental disorders? For example, how can multi-level longitudinal studies provide insights leading to the identification of *modifiable* risk factors? How can these approaches lead to the discovery of developmental windows of opportunity when early intervention can target a specific set of interacting biological and social processes in ways that can have a positive impact in particular sets of high-risk youth? How might these approaches ultimately contribute to the long-term goal of informing strategies at the scale of a population health (prevention) framework?

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Published online: 08 May 2015

Indeed, from a public health point of view, studies of etiological processes are primarily useful precisely because they can inform innovation and increased effectiveness in our prevention and treatment efforts. The foundational example from the history of public health is the combination of epidemiological and etiological insights that led to targeting the microbiological quality of drinking-water—and the subsequent worldwide impact on many important infectious and parasitic diseases, including cholera, typhoid, dysentery, hepatitis, giardiasis, guinea worm and schistosomiasis (Ashbolt 2004). A more recent illustrative example to consider focuses on the public health advances in preventing skin cancer. The combination of epidemiologic data (e.g., children with a history of sunburn show increased risk for developing skin cancer as an adult) and etiological understanding of the gene by environment interactions (e.g., fair skinned individuals living in environments with high degree of UV exposure from sunlight) has led to high impact prevention strategies: aggressive use of sunscreen and protective clothing, particularly in high risk (fair skin) children living in high-risk environments (Corbyn 2014; Kuhlmei et al. 2012). The primary point here is that the biological insights were leveraged to identify modifiable *behavioral* targets in real world settings (drinking clean water, protection from sun exposure).

On the one hand, it might sound a bit naïve (or overly optimistic) to imply that developmental research on emotional disorders could eventually lead to the identification of early intervention strategies aimed at modifiable targets in some ways akin to 'clean water' or 'protection from sun exposure'. On the other hand, we believe that there are key principles illustrated by these examples that have relevance to moving the field forward—particularly regarding the crucial value of multi-level etiologic understanding.

One perspective on these issues relevant to anxiety and depression in youth, is the US National Institute of Mental Health's Research Domain Criteria (RDoC) project, a framework that is increasingly being used to guide funding priorities, and that aims to provide exactly this kind of multi-level, mechanistic understanding of mental disorders by examining clinical phenomena and risk factors "across units of analysis ranging from genetics and circuit activity to psychology and behavior". Furthermore, and especially relevant to the readership of this journal, the RDoC seeks to understand "developmental trajectories through which these functions evolve over time, and the interaction of neurodevelopment with the environment" (Research Domain Criteria, 2015).

In this commentary, we would like to focus on three crucial aspects to making progress with this type of approach. First, the value of including an emphasis on biology (and specifically, translational neuroscience) in achieving etiological insights. Second, the role of developmental science in helping to identify windows of opportunity for intervening with modifiable risk factors. Third—and most relevant to the papers in this special section—the importance of an integrative multilevel understanding of key developmental processes. We believe that the greatest value of addressing a developmental neuroscience level of etiologic insights is *not* to 'biologize' complex disorders, but rather to leverage this biological level of mechanistic understanding as a way to bridge back to the real-world level of social, behavioral, and affective processes that can be modified during key developmental windows of opportunity.

In the next sections we will first, briefly consider how each paper in this special section provides examples of progress within this framework. Second, we will then describe a broader set of ideas and perspectives regarding ways to advance these approaches.

Papers in the Special Section

The paper by *Meyer* et al. highlights several features relevant to the points of emphasis in this commentary. This longitudinal, prospective study examined a specific developmental window (the interval from age 3 to 6 years of age). The study focused on observational measures of hostile parenting and self-report measures of authoritarian parenting style at age 3, and how these measures of harsh parenting uniquely predicted a well-characterized neurobiological measure of interest (ERN) in these children 3 years later. The choice of the ERN was based on a series of previous studies that have shown changes in error processing associated with anxiety disorders in children. The results demonstrated that both the observational and self-report measures of harsh parenting at age 3 predicted larger magnitude ERN at age 6. The authors also reported analyses showing that the ERN magnitude mediated the relationship between harsh parenting and child anxiety disorder. Taken together, these findings provide preliminary support for the idea that harsh parenting may shape some developing social-affective process in young children—one that presumably involves fast automatic responses to making errors—that contribute to risk for anxiety. As noted in the limitations of the paper, a good deal of additional work is needed to confirm and better understand these findings. In particular the question of whether abnormalities in the ERN truly mediate the relationship between environmental experiences and symptomatic outcomes is especially critical.

However, if replicated, and strengthened by deeper etiological insights, these findings could lead directly to identifying promising candidates for modifiable targets - specifically, parenting interventions aimed at high-risk youth. These findings also raise additional mechanistic questions about what specific aspects of harsh parenting might interact with specific aspects of social-affective processing. Clearly there is a need for a deeper understanding of related social-affective learning processes that might also influence this set of response systems

(as measured by ERN), which could provide further insights relevant to early intervention targets.

This set of findings also highlights the potential value of a strong developmental science framework to further extend this line of investigation. For example, how might we better understand the optimal developmental timing for modifiable targets suggested by these findings? Is there something specific about this 3–6 year old range? Might an earlier parenting intervention be equally, or more, effective in altering the development of these systems (and the development of anxiety)? Is there plasticity for positive change in this system that extends much further into childhood and adolescence as well? How might we best integrate a broad consideration of theoretical and normal developmental perspectives on this question of timing, as well as developmental social and affective neuroscience perspectives?

To return to a central principle described earlier, the goal here is not to simply 'biologize' the effects of harsh parenting at age 3 contributing to anxiety at age 6, but rather to gain mechanistic insights (e.g., a deeper understanding of the changes in error processing that appear to mediate the effects of harsh parenting) that may inform testable hypotheses about the specific targets (and optimal developmental timing) for early interventions aimed at high risk groups.

The paper by *Hastings* et al. examines the developmental window from age 4 to 8.3 years, using multilevel models within a bioecological framework to examine pathways to internalizing difficulties in a sample of 375 families drawn from three independent studies. By combining parallel data from three independent studies the authors gained greater power to detect multilevel effects, permitting them to examine the additive and interactive contributions of several factors relevant to children's development of internalizing problems. The study focused on measures of behaviorally inhibited temperament, cortisol (in response to the social stressor of meeting a stranger) and gender, as moderators of the links between mothers' negative parenting behavior, negative emotional characteristics, and socioeconomic status in the pathway to developing internalizing problems measured 5 years later (at age 8). Behavioral inhibition and lower socioeconomic status were directly predictive of more teacher reported internalizing problems.

One of the most interesting findings from this study was evidence that behaviorally inhibited girls appeared uniquely likely to benefit from the protective aspects of higher SES. The authors speculate: "reticence of inhibited girls to engage with unfamiliar social contexts might lead them to spend more time at home. If that home is provided by well-educated parents with well-paying, high-prestige jobs, they would likely be engaging with a safe and enriched setting." Again, with all the usual caveats about the need for replication and additional studies, this provides an example of a potential lead to a modifiable target (and probably also, the need for deeper, more mechanistic etiologic insights). For example, further characterizing the nature of the vulnerability from behavioral inhibition (e.g., greater reactivity to stress impacting specific aspects of neurodevelopment; or avoidance of social situations that interfere with social reward learning; or several other alternatives) as well as delineating what aspect of high SES confers protection, could lead to specific testable hypotheses.

The value of a deeper understanding of the relevant underlying mechanisms applies not only to the vulnerabilities relevant to BI and SES interactions, but also to their findings that prolongation of elevated cortisol in inhibited preschool-aged girls (after meeting adult strangers) was also associated with increased risk for developing internalizing problems. It is unclear for example, if this finding simply reflects differences in social evaluative threat response, or whether alterations in HPA function might contribute directly to negative developmental trajectories.

Finally, as in the previous study, there also appear to be important questions within the frame of developmental science: Are there specific reasons they have focused on this 5-year interval from 4 to 8? Would these findings suggest focusing on identifying specific developmental processes that could represent modifiable targets that might be leveraged during this window of maturation?

The study by *Giletta*.et al. presents intriguing evidence indicating that a biological measure (cortisol response to a laboratory social stressor) was predictive of suicidal ideation 3 months later in a sample of 138 adolescent females (M age=14.13 years) who were at risk for suicidal behaviors. At baseline, lifetime suicidal ideation and a number of risk factors were assessed (i.e., depressive symptoms, impulsiveness, pubertal status and peer stress). Compared to females in the normative cortisol group, females in the hyper-responsive cortisol group were at increased risk for reporting suicidal ideation 3 months later, after controlling for prior ideation. The authors also found some evidence that pubertal maturation also contributed to understanding the increased risk. Given the importance of identifying suicidal risk in adolescents as a target for high-impact early intervention, these findings are very interesting.

Within the larger framework of a developmental translational neuroscience framework, the study also raises many questions. At the simplest level, what are the underlying mechanisms of the high (and prolonged elevation) of cortisol in these girls? There is increasing interest in understanding the development of neural systems involved in social evaluative threat—particularly during adolescent development and particularly in relation to the development of anxiety and depression in girls during adolescent (see Silk et al. 2012; 2014; Spielberg et al. 2015).

In addition to the developmental social neuroscience framework for these questions, there are also important

psychological and methodological questions about assessing responses to social evaluative threat. For example, the Trier Social Stress Test has emerged as one relatively standardized approach in adults—yet there is considerable variability in the methods of administrating the TSST in children and adolescents. In part this is because children can find the adult version to be highly aversive, and altering the protocol to be kinder and more supportive can undermine the standardization of the social threat. The version of the TSST used in this study is innovative: participants were instructed to pretend to audition for a reality show about how teenagers make friends, and instructed to give a 3-min audition speech about this topic, immediately after a 1-min preparation period. During the preparation and the speech, participants were oriented towards a camera and to a closed-circuit feedback screen displaying their own live image and an adult male judge was present in the room with the female adolescent during the speech task, ostensibly evaluating the quality of their performance. As the authors explain, "the presence of an adult and opposite-sex judge was intended to increase the social-evaluative nature of the task…" However, this method also raises questions about the specific nature of social evaluative threat that is being experienced by adolescent girls at risk for depression and suicide (including their previous negative experiences with relationships, evaluation, threat, rejection, and other negative emotions). The fact that this version of the task identified a biologically measured risk factor for future suicidal ideation is no less interesting because of these issues, but it does raise questions about the specific psychological as well as biological differences that could contribute to greater social evaluative threat in this social situation.

The importance of a developmental science perspective is also highly relevant. The authors have specifically focused on pubertal maturation as an important developmental process relevant to their questions. As others have also discussed (Crone and Dahl 2012; Nelson et al. 2005; Pfeifer and Allen 2012) the social–reorientation at the onset of adolescence represents a period of vulnerability and opportunity for social-affective learning and there is a need to deepen our understanding of the neuro-maturational mechanisms that confer this vulnerability, and which may offer targets of opportunity for early intervention.

In the study by *Nederhof* et al., the authors analyzed longitudinal data from a large prospective population study of 715 Dutch adolescents (assessed at 16.3 and 19.1 years of age) focusing on reactivity measures of the hypothalamic pituitary-adrenal (HPA) axis and autonomic nervous system (including heart rate, HR; respiratory sinus arrhythmia, RSA; and pre-ejection period, PEP) in response to a social stress task. As the authors describe the effects of any single measure of reactivity had little predictive ability for concurrent or longitudinal changes in internalizing and externalizing symptoms. However, there were some intriguing interactions found between HPA-axis reactivity and sympathetic and parasympathetic reactivity, particularly in boys. Specifically, boys with high HPA reactivity and low RSA reactivity had the largest increases in internalizing problems from 16 to 19 years, and there also was a significant three-way interaction between RSA, PEP and cortisol predicting future externalizing problems in boys.

Among the major strengths of this study are: the large longitudinal sample, the rigor in performing the social stress test and in obtaining the autonomic measures, and the sophistication of the analyses. Viewed from the framework outlined in this commentary, the most prominent questions to emerge focus on how to bridge from these findings to etiological insights? It would be valuable to develop heuristic models as to how these combinations of reactivity are thought to reflect specific processes relevant to development of specific disorders. It is also not clear whether the authors are focusing specifically on this developmental window (late adolescence/transition to adulthood) and how/why changes in social stress reactivity at this maturational interval may create modifiable targets. There are also important questions regarding how to link these findings more directly to the developmental social and affective neuroscience models regarding social evaluative threat (as described previously).

The paper by *Guyer* et al. also exemplifies the points raised at the beginning of the commentary. This study used a prospective, longitudinal, multi-level approach to assess the interwoven relations among temperament, family processes, peer responses in adolescence within a developmental cognitive, affective, and social neuroscience approach aimed at etiologic insights about social anxiety.

The sample has been followed from toddlerhood into adulthood, is based in well-established theory focusing on Behavioral Inhibition (BI) as a temperament at greater risk for developing internalizing disorders, and is testing an interesting set of hypotheses about parenting and peer rejection in adolescence. Specifically, the authors used functional neuroimaging to assess the moderating effects of authoritarian and authoritative parenting styles on neural response to peer rejection in adolescents characterized by their early childhood temperament. They found that in youth with BI (but not in those without BI) diminished responses to peer rejection in ventrolateral prefrontal cortex (vlPFC) were associated with higher levels of authoritarian parenting. In contrast, both groups (those with BI and without BI) showed decreased caudate response to peer rejection at higher levels of authoritative parenting. These findings are consistent with hypotheses that behavioral inhibition in early life creates greater neurobiological sensitivity to harsh parenting as evidenced in neural responses of to peer rejection in late adolescence.

As the authors discuss, this set of findings, taken together with several other studies of neural responses to social anxiety and to peer rejection in adolescents, suggest that positive

parenting may help to buffer the salience of negative peer experiences in youth who might otherwise be at greater risk for developing internalizing disorders. If replicated and extended, this set of etiological insights suggests specific targets for early intervention among children with behavioral inhibition. The studies also raise a series of questions about mechanism and the optimal developmental window to target for these interventions. Moreover, given that several papers are consistent with the idea that harsh parenting is an important candidate as a modifiable target, we will return to a broader set of questions focusing on parenting in the last section of this commentary.

Each of the papers in this special section contributes important steps toward the task of providing a compelling, multilevel, developmentally informed, model of the etiology of internalizing disorders in children and youth. We have also noted how important it is to extend and deepen this work in order to fully achieve the potential impact of these studies. In the following section we would like to consider a broader view of this translational framework, primarily to help place these studies into a larger research context, and to help guide future efforts to advance the field.

Frameworks for Translational Neuroscience

Given the inclusion of biological variables in the papers in this special section, and the emphasis placed on such measures in the discussions about translational efforts in mental health, we would like to start by considering the specific example of translational neuroscience. Translational Neuroscience in mental health can be defined as basic science studies that are conducted with the specific intent to *discover* mechanisms, biomarkers, etiological factors or treatments for mental disorders, or clinical studies that provide a foundation for developing, or that directly test, *novel* therapeutic strategies for people suffering from mental disorders. (McArthur and Borsini 2008). The emphasis here has to be on the terms "discover" and "novel", which imply that in the strongest form of translational neuroscience, neuroscientific and other biological data should make a novel contribution, whereby findings from studies of neurobiological processes change what we do in the clinic (or community) - not just "biologizes" what we do anyway (as noted above). This is not a trivial hurdle to pass – in fact many would say that none of the variables studied in the papers in the special section (neuroimaging, neuroendocrine, autonomic, phenotypic temperament measures) have yet truly met this challenge, despite a dramatic increase in our understanding of the role of these processes in mental health disorders (Insel 2009).

In order to move things forward, and to improve our efforts to leverage neuroscientific and other biological data to make a real difference in treatment, prevention and public policy directed at improving mental health, it is valuable to be clear about the different ways in which these data might be translational, so that we can clearly judge both the aims of specific studies, as well as the translational potential of their actual findings.

The Traditional (Biological Psychiatry) View of Translational Neuroscience

Perhaps the most fundamental view of translational neuroscience is that associated with the field of biological psychiatry and related disciplines. In this view research aims to discover fundamental biological processes (i.e., neurochemical, neurophysiological, genetic) that show such a strong causal relationship to the onset or maintenance of mental disorders that modifying these through various means (e.g., pharmacological, neurostimulation, neurosurgical) will reliably result in the reduction or prevention of symptoms. Despite the obvious effectiveness and pervasiveness of psychopharmacological approaches to mental disorders, many have argued that these approaches have stagnated in recent decades, and moreover, have not been significantly informed by the explosion of neuroscienfic research during this period. For example, Thomas Insel, the Director of NIMH has argued that,

> "Despite high expectations, neither genomics nor imaging has yet impacted the diagnosis or treatment of the 45 million Americans with serious or moderate mental illness each year. While we have seen profound progress in research (with molecular, cellular, and systems neuroscience revealing new, unexpected insights about the brain), the gap between the surge in basic biological knowledge and the state of mental health care in this country has not narrowed and may be getting wider." (Insel 2009)

Furthermore, Akil has concluded that :

> "Unfortunately, there have been no major breakthroughs in the treatment of schizophrenia in the last 50 years and no major breakthroughs in the treatment of depression in the last 20 years. Over the last few decades, drug treatments have emerged that help a subset of these patients, but a sizable proportion are resistant to all currently available treatments." (Akil et al. 2010).

The exact reason for the difficulty in translating neuroscientific findings into effective treatment and preventative strategies is a matter of speculation, but we would argue that a few of the critical issues relate to 1) the low likelihood that specific biological factors have a sole causal role in the onset or maintenance of mental health problems, and 2) the lack of methods that allow us to powerfully, and (more critically perhaps)

precisely, modify biological processes. This results in a situation whereby biological intervention based on neuroscientific findings are often attempting to reduce symptoms via manipulation of one aspect of a complex, highly interconnected, multi-part system, and accordingly the association between manipulation of these variables and symptoms is less predictable and powerful than would be ideal. Furthermore, due to the relative lack of precision with which our biological intervention tools (e.g., pharmacotherapy, brain stimulation therapies) can manipulate these variables, treatments often have significant side effects that in some cases can verge into the unethical (e.g., in the case of psychosurgery).

A related view of translational neuroscience worth noting is what might be called the "*basic science fundamentalist*" view. In this approach, some argue that is it foolish to try to make neuroscience intentionally translational, as such efforts will only stifle creativity and perhaps divert resources away from important fundamental science. This view asserts that we cannot know exactly which findings will ultimately become transitional, and that the primary responsibility of scientists is to discover the laws of nature as they apply to brain-behavior relationships, and that it is only through pursuing this agenda that truly transformational discoveries will be made. This idea is rooted in some spectacular examples of the unexpected translational potential of basic research in the past (admittedly many are drawn from engineering and the physical sciences rather than health care), however as the evaluations above suggest, this approach too has yet to produce truly impactful findings in mental health.

The Intermediate Phenotype (Cognitive Neuroscience) Approach

In the effort to recognize the fact that causal relationships between biological processes and mental health may be profoundly mediated or moderated by other variables, some have advocated an approach that emphasizes understanding the relationship between biological process and modifiable intermediate phenotypes (i.e., psychological or other phenotypic mediators of the relationship between biological processes and symptoms of mental disorder; Meyer-Lindenberg and Weinberger 2006). One particularly notable variant of this approach has been to emphasize discovering strong relationships between neurobiological processes and cognitive phenotypes that are thought to underlie symptoms. An example of this is studies of working memory deficits, and their association with vulnerability to various mental disorders such as schizophrenia or ADHD (Andrews et al. 2011), explicit training in self control (Berkman et al. 2012), and work on attention bias retraining for anxiety disorders (Hakamata et al. 2010). Here the emphasis is on brain-cognition relationships that are hypothesized to be so strongly coupled that interventions designed to modify cognitive processing are predicted to have effects on brain function (and perhaps over time, structure) as well as reducing mental health symptoms.

Although this approach has spawned some very interesting new approaches that involve cognitive training methods that aim to modify key putative psychological (especially cognitive) mechanisms, there have been some questions raised about the effect sizes associated with these methods (Hallion and Ruscio 2011) especially as they relate to case level disorders (Cristea et al. 2015). Another shortcoming of these approaches is that they often fail to fully integrate the critical role of interpersonal and environmental factors in the onset and maintenance of mental health symptoms. Indeed, a number of the papers in the current issue demonstrate the critical role of parenting in risk for internalizing symptoms and related biological processes (i.e., Meyer et al., Guyer et al.,, Hastings et al.,), and furthermore demonstrate how the interpersonal and environment factors can correlate, and interact, with biological processes to increase risk for internalizing disorders. As such, intermediate phenotype models may miss the opportunity to leverage a range of environmental interventions, be those associated with parenting processes, family environment, or policy intervention aimed at enhancing developmental environments.

The Construct Validity (Nomological Network) View

This final approach suggests that biological and neuroscientific data do not have a privileged position with respect to uncovering the fundamental mechanisms responsible for mental disorders, nor do they necessarily suggest that biological methods of intervention are the most effective. Rather, the Construct Validity view suggests that biological data form a critical, but not privileged, component of a nomological network describing the clinical phenomena of interest.

Lee Cronbach and Paul Meehl originally proposed the concept of a nomological network in 1955 as a method of evaluating the construct validity of psychological tests (Cronbach and Meehl 1955). In order to provide evidence that your measure has construct validity, they argued that you had to develop a nomological network for your measure, which consisted of both a theoretical framework and an empirical framework regarding methods of measurement, and specification of the links among and between these two frameworks. In applying these ideas to the understanding of vulnerability to clinical disorders, often biological and neuroscientific data form a critical component of providing construct validity to proposed mechanisms - not because these mechanisms are necessarily purely biological in nature, but rather because valid etiological mechanisms will presumably be represented at multiple levels and within a variety of kinds of data. This is especially relevant to psychological and behavioral mechanisms that cannot be validly assessed via self report (which is probably most of them), where neuroscientific and other

biological data can provide strong inferences regarding the action of such mechanisms.

The importance of this view is that, as stated above, it does not see biological processes as privileged data, or more "real" than other kinds of data in terms of their causal status, but nevertheless suggests these kinds of data are critical to fully and convincingly establishing the validity of those mechanisms. Once mechanisms strongly associated with the onset and maintenance of mental disorders with a high degree of construct validity (as suggested by empirical support from a nomological network that includes measurements at multiple levels or analysis) have been established, then potentially modifiable elements of these mechanisms can be identified. As noted above, we will want to identify variables where the strength and specificity of methods of modification are strong, such that we have valid and ethical means for modifying these processes. Furthermore, public health concerns will also necessitate that we consider issues of dissemination and implementation – methods that cannot be efficiently delivered to those who are most at need, or across a large enough proportion of the population, are inherently less useful (e.g., using neuroimaging for mass screening to identify high risk individuals). Sometimes these considerations might point to a biological method of intervention, but psychological, environmental and public health interventions are just as valid outcomes of this form of "translational neuroscience" if they meet the above criteria most effectively. In this sense the translational aspect of most biological data is not specifically to discover biological mechanisms, but rather to provide critical construct validity data in the description of multi-level mechanisms, which can then be used to identify the best levers for intervention. These can potentially be modified through a variety of techniques that may target different levels of the mechanism, depending on the tools available.

Translational Developmental Science

A more recently emphasized aspect of translation science that is particularly relevant to these studies, and this journal, is the role of understanding development as a moderator of treatment effects. Neuroscientific and other research has identified sensitive periods for the effects of learning, stress, and other environmental exposures on the development of human capacities, including risk and resilience (Andersen and Teicher 2008). This suggests that developmental plasticity associated with these sensitive periods may be a key moderator of intervention effects, in both prevention and treatment contexts, such that interventions may have greater effects when they target processes during such developmentally plastic periods.

A related concept is that of developmental sequencing of intervention effects, which suggest that some interventions may rely on the emergence of particular psychological capacities before an individual can fully benefit from the learning opportunities offered by exposure to the intervention. For example, some have argued that cognitive intervention techniques might be less effective for children or adolescents until they have achieved a certain level of cognitive development that allows them to effectively access and utilize these techniques (McCauley et al. 2011). Both the sensitive period and developmental sequencing perspectives suggest that developmental processes may be an important missing component in the targeting of intervention efforts. Although the recognition that developmental processes affect treatment outcomes is rife in clinical folklore, there are few clearly articulated treatment guidelines that provide a strong empirical basis for targeting treatment or prevention programs at particular stages of development. This is probably in part due to the fact that our typical way of quantifying maturation, via chronological age, is fairly imprecise, especially during adolescence when individual differences in the timing and tempo of puberty and neurodevelopment can result in dramatically different levels of maturation amongst individual of the same age. Accordingly, work that identifies a multi level description of maturation, and that on the basis of that identifies methods of quantifying maturation that more specifically predicts response to developmentally interventions, may be a specific example of a way in which a biologically informed construct (i.e., maturation) may be used to identify critical issues in the design, planning and delivery of interventions.

Parenting as a Translational Developmental Neuroscience Intervention Target

A key theme in a number of the papers in this special section is the role of parenting in predicting both internalizing symptoms and neurobiological risk factors. Accordingly, we would like to close this commentary by briefly exploring how parenting may be a key example of a neurobiologically and developmentally informed translational target for intervention. A wide range of family factors have been investigated in relation to internalizing problems during childhood and adolescence (Schwartz et al. 2012; Sheeber et al. 2001). In particular, affective processes and behaviors during parent–child interactions have been identified as important and potentially modifiable risk factors that may be useful targets for preventive interventions (Eisenberg et al. 1998; Morris et al. 2007). For example, both cross sectional and prospective associations between observed parenting behaviors during early- to mid-adolescence and a range of internalizing outcomes have been demonstrated (Schwartz et al. 2012; Sheeber et al. 2001). Furthermore, this risk factor shows developmental specificity as indicated by the observation that patterns within family interactions show dramatic developmental change across the child's lifespan, including a peak in parent–child conflict that

occurs during early adolescence and therefore directly precedes the dramatic increase in the incidence of depressive disorders that occurs in early to mid adolescence (Laursen and Collins 1994). As such parenting presents itself as a key potentially modifiable target for both prevention and intervention. One may ask then, given these findings, in what way does neuroscientific data contribute to motivating parenting as a translational target?

According to the Construct Validity approach to translational neuroscience outlined above, it is not enough to simply identify a correlational relationship between a modifiable risk factor and a mental health outcome in order to justify it as a strong target for intervention (even if the correlation is prospective and longitudinal). Indeed, intervention research, not just within psychology and psychiatry but also in medicine generally, is littered with examples of correlational risk factors that turn out to have no causal status and are therefore ineffective levers for intervention. For example, homocysteine is an amino acid that is linked to heart disease, and this correlational observation motivated doctors to prescribe various B vitamins to reduce homocysteine. However, a subsequent meta-analysis showed that the treatment had no effect on the risk of heart attack or stroke, despite the fact that homocysteine levels were lowered by nearly 25 % (Clarke et al. 2010), thereby spectacularly endorsing the old adage that correlation is not causation. Because of these problems with identifying powerful and valid intervention targets, data that provide extra construct validity in terms of identifying potential causal pathways and mechanisms by which a risk factor might influence outcomes are particularly important. For example, previous recent research has shown that aspects of the family environment can influence brain development (Whittle et al. 2014) and immune functioning (Miller and Chen 2010), both of which are plausible pathways to internalizing disorders, especially depression. Papers presented in this special section further extend the nomological network around parenting, providing extra construct validity for this risk factor by demonstrating that parenting predicts changes in brain function that can plausibly be related to risk mechanisms (Guyer et al., Meyer et al.), or that the relationship between parenting and internalizing symptoms is moderated by relevant biological processes (Hastings). These data therefore place parenting in a nomological network of information that increasingly strengthens its validity as a causal mechanism, and therefore a target for intervention. Of course, the case is not yet proved, and ultimately requires experimental (i.e., intervention) studies that track not only the impact on internalizing and other mental health outcomes, but also demonstrates change in plausible biobehavioral mechanisms by which the intervention achieves its effects. Finally, the developmental perspective also requires that we demonstrate not just *whether* an intervention works, but also *when* in development it is most effective at altering risky trajectories and therefore improving outcomes. Nevertheless, the data presented herein further contribute to the case for parenting as a key lever in the prevention and treatment of internalizing disorders by enriching our understanding of the multi level effects of these processes, and therefore providing a more mechanistic account of etiology that can us used to generate and refine intervention strategies.

Conclusion

We have discussed the articles in this special section with an emphasis on the specific utility of these kinds of multivariate, multi-level models in developmental psychopathology for ultimately contributing to etiologic insights and translational advances that make a real difference in the lives of children and adolescents vulnerable to internalizing mental disorders. We have considered these issues not only in terms of these specific papers, but also within a larger set of questions regarding the opportunities (and challenges) currently facing the field. We believe this an exciting time for integrative team-science approaches to tackle these challenges—a time that holds great promise for rapid advances in integrative developmental science that includes a biological level of mechanistic understanding. Ultimately, these kinds of investigations will provide etiologic insights regarding real-world targets at the level of social, behavioral, and affective processes that can be modified during key developmental windows of opportunity.

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Conflict of Interest Neither author declares any conflict of interest with respect to this manuscript.

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