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Developmental psychopathology: recent advances and future challenges

SETH D. POLLAK

Department of Psychology, University of Wisconsin-Madison, Madison, WI 53706, USA

The integrative field of developmental psychopathology is having a huge impact on our understanding of human health and behavior. In this paper, I use the example of children's early stress exposure to illustrate how developmental psychopathologists now tend to deemphasize diagnostic categories and, instead, emphasize the social and biological contexts, events and circumstances that have created opportunities for maladaptive responses and health problems in youth. This example shows that developmental psychopathology is increasing understanding of how children develop the abilities that allow them to cope effectively with challenges and what leads to failures in development of these abilities. Integrating research about the neurobiology of learning may prove to be a powerful future direction to understand how the environment regulates behavior. Learning processes become increasingly intricate and fine-tuned as relevant neuroanatomical systems develop, and as the range, complexity and amount of environmental information increases for the developing child. A focus on these processes allows psychopathologists to formulate questions about which neural mechanisms children use to process information, how these mechanisms are themselves shaped by social context, why adverse social environments confer risk for children, and, perhaps, what sorts of neutrally informed interventions might remediate the deficits in self-regulation that underlie common psychopathologies.

Key words: Developmental psychopathology, child stress, child psychiatry, child maltreatment, depression, child development, attention, learning

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Developmental psychopathology, as an integrative field of study and scientific approach, is just a few decades old. But it has already had a huge impact on our understanding of human health and behavior (1). The popularity and prominence of the approach has risen quite rapidly and has fostered connections between many fields of study, encompassing cross-cultural perspectives as well as new methods from the neurosciences. In this paper, I will illustrate some of the ways in which the developmental psychopathology perspective has shown utility for the field of psychiatry, highlighting recent trends and future challenges.

Psychiatrists have long been concerned with individual differences in how youth with behavioral problems manifest clinical symptoms, as well as differences between individuals in their responsiveness to treatments. But, at the time developmental psychopathology began to emerge, the field of psychiatry was very focused on diagnostic issues. Child psychiatry was concerned with topics that included formulations of taxonomies for mental disorders, the relations between those categories, and the bases for determining if an individual met criteria for a particular diagnosis. In more recent years, psychiatric research has begun to consider “biomarkers” associated with various forms of pathology as a way to reconcile diagnostic taxonomies with biological systems. But, despite the many publications correlating a diffuse array of biomarkers with various forms of psychopathology, no individual biomarker has yet emerged as a discrete entity that has been shown to account for a sufficient proportion of variance in behavior, or that is sensitive or specific to behavioral disorders.

It is in this regard that the developmental psychopathology approach holds promise. In isolation, markers (e.g., functional

brain activities, hormonal assays, genetic markers, or cognitive test scores) are merely *correlates* of behavior problems. In contrast, developmental approaches seek to understand the *processes* by which these components have emerged and become integrated across biological, psychological and social contexts over the individual's life course. This approach leads to the dissolution of the distinction between mental and physical disorders, and can especially be seen with regard to understanding children's responses to stress. The approach has also manifested itself with a renewed emphasis among researchers on the interactions between persons and their environments. I will illustrate some of these principles using the phenomenon of child maltreatment as an example of severe early life stress exposure.

Child maltreatment predicts both unfavorable mental health outcomes as well as poor responsiveness to mental health treatment (2). Maltreated children are at risk for developing externalizing behavioral problems characterized by reactive aggression. For example, these children exhibited greater negative affect in response to an interpersonal stressor, which was subsequently associated with more aggressive behavior towards their peers. This relationship was mediated by children's allocation of attention to angry faces as measured by brain event-related potentials (3). These data suggest that physical maltreatment leads to inappropriate regulation of both negative affect and aggression, which likely places maltreated children at increased risk for the development and maintenance of externalizing behavior disorders.

Yet, child maltreatment is also associated with heightened risk for mood disorders, though not all individuals who experience maltreatment develop depression or anxiety. One clue about the ways in which the early experience

of maltreatment may lead to depression can be found in observations of maltreated children's attention bias for emotional cues (4). A recent study reported that maltreated children showed attentional biases to depression-relevant cues in certain conditions: first, after they had experienced a sad emotional state, and second, if they tended to have high levels of trait – or stable – cognitive patterns of rumination (5). These patterns may identify which maltreated children are at heightened risk for depression.

The phenomenon of rumination – passively and repetitively dwelling on and questioning negative feelings in response to distress – is a known risk factor for the development of psychopathology, especially depression (6). Recent research in a community sample of 9 to 14 year olds showed that it was common for youth to focus on an interpersonal stressor for a brief period of time after experiencing it; yet about 10% of the youth continued to ruminate for a long period of time after the stressor ended (7). Although most participants were able to disengage from this type of ruminative thinking, those individuals who continued to ruminate showed attentional biases away from positive stimuli (7). Thus, these children actively avoided environmental cues that might have helped them regain a positive mood state and recover from the stressful event. Consistent with this view, rumination in adolescents is associated with difficulty inhibiting negative information when switching from processing of negative to positive information (8). The ruminative process is difficult to stop once it has begun. But relatively straightforward interventions, such as brief periods of distraction or mindfulness, appear to be helpful in getting children out of ruminative states (9).

Of concern, however, is not just internalizing and externalizing psychopathology, but also sub-clinical problems that decrease children's quality of life, such as emotion regulatory difficulties, problems with social competence, factors that interfere with optimal school performance, as well as factors that affect physical health. Attention to these issues reflects the increasingly broad focus on the whole child, rather than psychiatric diagnoses in particular, within developmental psychopathology.

A FOCUS ON DEVELOPMENTAL PROCESSES

Some developmental psychopathologists continue to professionally identify according to the diagnostic category they study (labeling themselves, for example, as “depression researchers” or “autism researchers”). But one noteworthy trend in the field is that, increasingly, younger generations of scholars are identifying themselves in terms of etiological and developmental mechanisms rather than discrete disorders. For example, these scientists may think of themselves as “stress researchers”, “affective neuroscientists” or scholars of “mind-body interactions”. In my view, such a change is not trivial and reflects a critical shift in emphasis among psychopathologists to link brain-behavior relationships to

dimensions of maladaptive behaviors (see 10-16). While researchers continue to study issues such as dysregulation of mood, they increasingly construe their topics as perhaps broader than “anxiety” or “depression”. And this reflects a major trend in the field to focus on maladaptive processes of change.

One reason for this change in emphasis is that it is now apparent that development is best characterized by probabilistic pathways rather than by linear causality. There has been no evidence that early adversity leads ineluctably to pathology. Rather, social and biological challenges initiate processes that may more likely lead to pathology if that maladaptive pathway continues to be supported. In this regard, developmental psychopathologists have become less focused on discrete causes of disorders. Instead, we are attempting to understand what places a child on one developmental pathway versus another, what constrains the individual's ability to alter these pathways, and during which developmental time periods, or circumstances, opportunities for change might be greatest.

DISSOLVING DISTINCTIONS BETWEEN MENTAL AND PHYSICAL HEALTH

An unintended effect of focusing on processes versus discrete disorders has been a blurring, with developmental psychopathology, of traditional disciplinary boundaries. Methods and concepts from fields such as psychiatry, psychology and pediatrics have come into greater contact with those from internal medicine, immunology, endocrinology, epidemiology/population health, and genetics. For example, research on children's responses to trauma and stress still includes issues such as anxious and aggressive symptoms, but also includes foci such as sleep, physical growth and bone density, allergy/asthma, infectious disease, and cancer vulnerability (17-22). In other words, mental health problems are being understood and linked with indicators of physical health, eroding the distinction between mental and physical ailments.

It has now become apparent that early life stress can compromise development, with higher amounts of adversity linked to a diffuse array of developmental problems. There is evidence that an important facet of risk for mental illness can be understood as altered neural processing of social stimuli, which impairs regulatory processes. This research both informs our understanding of the emergence of health problems in children and adults, and also sheds light on principles of normative development. In this manner, we increase understanding of how is it that children's social experiences subsequently shape their thoughts, feelings, biology and behavior.

One lens for understanding the principle of development is the rubric of learning. The history of psychology is rich with examples of the immediacy and power of basic learning processes. For example, we need only become ill once to

create a strong food aversion, and changes in the frequency of reward schedules can quickly change behavior (23). Indeed, reward learning is currently a central topic of exploration among psychopathologists (see 24). Rodent studies have provided compelling evidence that learning theories can uncover rich information about the neurobiology of socio-emotional behavior. For example, experimental disruption of reward circuitry in the brain prevents mice pups from emitting vocalizations when removed from their mothers. Interfering with brain reward systems also prevents mice from showing a preference for their own mothers (25).

This association also works in the opposite direction: when attachment to the parent is disrupted, other aspects of the animals' reward systems are also affected. To illustrate this point, animals with disrupted attachments to their parents also have abnormal responses to novelty, altered appetitive conditioning, and unusually high sensitivity to dopamine antagonists and reactivity to other drug administrations (see 26,27). Such findings have also been extended to studies of children with disruptive behavioral disorders (28).

Similar types of effects are becoming evident with regard to the emotional development of school-aged children who have had adverse early experiences. Children who have suffered from physical abuse are exposed to inconsistent or poorly conveyed emotional signals in their environments. The adults who ought to be responsible for these children's care tend to vacillate between extreme emotional states of anger and social withdrawal (29). Yet, these social interactions with primary caregivers are the primary basis upon which these children begin to learn about their social environment. For this reason, greater understanding of the brain regions associated with learning reward or punishment is likely to help account for the effects of the environment on these children's interpersonal behavior.

Children who have been physically abused become adept at recognizing cues of anger and hostility (3,30,31). These patterns reflect ways in which children learn to direct their attention to salient and meaningful information in the environment. This type of attention to threat cues in the environment subsequently affects the way children come to construe their social worlds. As an illustration, 5-year old abused children tend to believe that almost any kind of interpersonal situation could result in an adult becoming angry; in contrast, most non-abused children see anger as likely only in particular interpersonal circumstances (32).

These types of data have raised new questions about how probabilistic information about other people's behaviors becomes instantiated in children's thinking. Given that children have a limited processing capacity and that there are limitless aspects of the world that can be attended to at any given moment, it may be the case that abused children prioritize negative social cues at the expense of positive cues. Consistent with this view, on a probabilistic reward task, most children responded quickly as their chances of winning a reward increased. In contrast, maltreated children were not sensitive to the likelihood of reward (33). And pri-

mate models also report that maltreated monkeys display less interest in rewards relative to control monkeys (34). A few candidate brain systems have emerged as potentially underlying these phenomena and provide clues about the development of psychopathology.

CANDIDATE NEURAL SYSTEMS IN DEVELOPMENT AND STRESS

The brain areas that currently receive the most attention from developmental psychopathologists include the prefrontal cortex (a likely candidate because of its protracted period of postnatal development, as well as ties to behavioral regulation abilities such as impulse control and executive functions), the amygdala (because of ties to emotional regulation), and the basal ganglia and orbitofrontal cortex (which, together, seem to represent the outcomes of situations that the organism has experienced) (see 35).

Much current research has been focused on the role of stress on children's cognitive abilities, specifically executive functioning, dependent on the prefrontal cortex. While descriptive studies in children and adults who have experienced specific types of maltreatment are important and informative, many research groups have begun to focus on the idea that it is not specific experiences, such as physical abuse, that affects biobehavioral development, but rather more generally stress and/or instability in children's lives (e.g., 36). A powerful example of this comes from the study by Hanson et al (37), who found that adolescents with high levels of cumulative life stress tend to have smaller volumes in the prefrontal cortex, specifically prefrontal gray and white matter between the anterior cingulate and the frontal poles. Moving beyond simple correlative analyses, this work also revealed that individual differences in prefrontal volumes accounted for the association between cumulative life stress and spatial working memory.

There has also been much research attention, but just as much inconsistency in findings, regarding the amygdala and its role in emotional dysregulation. The divergence in findings may stem from methodological factors, heterogeneous samples of at-risk children, nonlinear effects of life stress, or a combination of all three. To address some of these issues, Hanson et al (38) completed rigorous hand-tracing of the amygdala in samples of children who experienced different forms of early stress, including physical abuse, early neglect or extreme family poverty. They found smaller amygdala volumes in children exposed to these different forms of stress, with brain development associated with both greater cumulative stress exposure and the emergence of child behavioral problems. These data suggest that early and severe life stress may be associated with increased excitation and cell death, reflected in reductions in brain volume. However, caution must be used when inferring developmental patterns from cross-sectional studies; only longitudinal research can truly validate such a model of amygdala

development after early stress exposure. Structural and functional alterations in the amygdala may help us understand individual differences in risk and resilience to behavioral problems as related to toxic stress.

The basal ganglia is a diverse network of subcortical structures that work in concert to orchestrate and execute planned, motivated behaviors that require integration of movement, thinking and feeling (39). The orbitofrontal cortex is a rapidly flexible associative-learning area that is crucial for signaling outcome expectancies such as reward/punishment and the regulation of flexible behavior (40). Current thinking is that the basal ganglia guide learning based on assessments of the probability of a positive outcome, while the orbitofrontal cortex represents gain-loss information and, together, these systems provide a robust way for the organism to learn from and adapt to the environment (41). As expected, impairments in these systems are associated with poor learning from environmental cues. It is especially interesting that orbitofrontal cortex neurons do not stop firing in response to the reward after learning, suggesting that these neurons support predictions on the basis of afferent input and anticipation prior to other emotion-processing regions such as the amygdala (42).

Consistent with this view, damage to the orbitofrontal cortex causes deficits in reversal learning, reduces the speed of reward learning, and is activated in humans during processes such as regret and counterfactual reasoning (43-45). Common to these examples is the need to signal, in real-time, information about outcomes predicted by circumstances in the environment. Some emerging evidence suggests functional changes in the orbitofrontal cortex and basal ganglia during reward processing in adolescents. This further suggests that these systems are a source of developmental changes in social behavior (46).

There is also some evidence that functioning of these systems may account, in part, for how early life stressors confer pervasive lifetime risks for children. Many kinds of early life stressors (maternal separation, social defeat, chronic stress exposure, abuse) appear to alter neurotransmitters and receptors in the basal ganglia that are subsequently associated with impairments in learning (47). Child maltreatment has been associated with lower basal ganglia recruitment during a reward task (48), and children who experienced early life stress have smaller orbitofrontal cortex volumes (49).

What developmental processes might link these components of neural circuitry? One well-understood system is the hypothalamic-pituitary-adrenal (HPA) axis, which is central for understanding the negative effects of stress and trauma on children. When an individual encounters a stressor, corticotropin releasing hormone (CRH) is secreted by the hypothalamus. This hormone acts on the pituitary gland, causing it to release adrenocorticotrophic hormone (ACTH). ACTH then acts upon the adrenal gland, resulting in the production of cortisol. Cortisol binds with glucocorticoid receptors in the hippocampus to regulate the HPA axis and inhibit further release of CRH. Similarly, cortisol re-

leased in response to stress binds with glucocorticoid receptors at the cellular level to regulate the immune system (50). This system promotes adaptation in response to normative stressors. Toxic or extreme levels of early life stress exposure may impair this system (51).

Other hormone systems also hold potential for understanding how early life adversity affects subsequent social behavior. For example, a recent study examined functioning of the neuropeptide oxytocin in children aged 8-11 years following a social stressor. Girls with histories of physical abuse showed higher levels of urinary oxytocin and lower levels of salivary cortisol following the stressor when compared to controls (52). Abused and control boys, however, did not differ in their hormonal responses. These data suggest that early adversity may disrupt the development of the stress regulation system in girls by middle childhood. Disruptions of this system have implications not only for children's successful regulation of emotion, but also for aspects of comforting behaviors such as the establishment of stable and secure interpersonal relationships.

From a developmental perspective, it is important to emphasize that enhanced threat detection (as well as the myriad systems that children use to promote self-regulation and comforting) are critical for children living in contexts that do not provide adequate protection. Thus, hormone systems such as glucocorticoids and oxytocin that play a role in coordinating these responses (53) may be important targets for interventions aimed at improving children's adjustment.

Accordingly, one of the most promising advances has been the use of epigenetic approaches to understand emotion regulatory processes. Epigenetics may well provide new traction in understanding etiological processes in a range of psychological disorders. We used to think of inheritance in terms of the letters of the DNA code passed from parents' egg and sperm. But now we know that there is another path: parental behavior can write information onto DNA completely bypassing egg and sperm. This adds a level of flexibility to extend a fixed DNA code. This biological flexibility seems quite logical: through experience, individuals use information about the world they are growing up in, changing DNA to cope with the environment.

Not only might actual characteristics of the environment affect gene functioning. It is also possible that children's interpretations and subjective perceptions of their experience is enough to trigger epigenetic changes (54). Given that the behavioral problems of maltreated children are largely accounted for by experiential rather than genetic risk factors (55), this dovetails with observations that maltreated children overly attend to threat/hostility in their environments. Such attentional processes may reflect short-term adaptation to hostile environments, but carry long-term risk for health and behavior.

Although the mechanisms through which these effects are achieved likely involve diverse cellular and molecular pathways, there is emerging evidence supporting the hypothesis that epigenetic changes, such as DNA methylation and

histone modifications, may mediate the effects of early life variations in the social interactions between mothers and infants. Moreover, there may be plasticity within these epigenetic pathways at later developmental time points, such that the social experiences of juveniles and adults may also induce epigenetic change (see 56). These findings have implications for understanding the emergence of behavior problems in early childhood (such as emotion regulation problems) as well as distal problems in adulthood (such as cancer and cardiovascular disease). These data also highlight the dynamic interactions occurring between genes and environments during the course of development.

Recently, epigenetic changes in the glucocorticoid receptor gene were examined by Romens et al (57) in whole blood from children aged 11-14 years. The promoter region of the gene is the sequence needed to turn the gene on and off. It is usually found near the beginning of a gene, and has binding sites for enzymes that make RNA. In the study by Romens et al, abused children had more methylation on several sites within exon 1F of the promoter region of the NR3C1 gene, especially CpG site 3, which may have important implications for brain development, given that it is the binding site for nerve growth factor (58).

These results highlight molecular mechanisms linking childhood stress with biological changes that may lead to mental and physical disorders. Consistent findings across both rodent and human studies suggest that better parental care decreases methylation of the glucocorticoid receptor promoter, increasing the expression of the receptor. Increased expression of the glucocorticoid receptor in the hippocampus reduces stress responsiveness. Though this is an oversimplified explanation (other factors are involved, such as chromatin and histones), the general idea is that methyl inhibits gene transcription and can be thought of as a useful framework for understanding the complexities of gene expression.

But translation across species is difficult. The current glucocorticoid receptor epigenetic data are consistent with the view that genes can be turned on and off; yet such studies in humans cannot infer causality and are limited in terms of specificity of the cellular processes occurring in the brains of living children. They also do not reflect gene expression. What the animal studies can do is to control for confounding variables that are not possible to account for in studies of humans, where we need to be opportunistic in our research.

One clear link between the controlled animal studies and peripheral measurement of epigenetic changes in humans concerns effects of early stress on immune system competence. Indeed, consistent with peripheral changes in methylation of the glucocorticoid receptor gene, children with early stress exposure show deficits in immune functions (17,22).

CONCLUSIONS

Recent research in developmental psychopathology has increased our understanding of how individuals develop the

array of capacities that allow them to cope effectively with challenges posed by each developmental period. This approach is also uncovering new insights into what leads to failures in development of these abilities. In this paper, I have used the example of children's early stress exposure to demonstrate how developmental psychopathologists now tend to deemphasize diagnostic categories and, instead, emphasize the social and biological contexts, events and circumstances that have created opportunities for maladaptive responses and health problems in youth.

Developmental psychopathologists have been less focused on causes of psychopathology and have tried to excavate processes of change. What leads an individual to adopt one pathway of development versus another? From this corpora of scholarship, two useful heuristics emerge. The first is that risk for psychopathology is cumulative. We now understand that aberrant early development of relatively simple skills early in life creates a weak foundation for more complex, later-emerging skills. Similarly, early challenges are likely to build and accumulate over the life course, increasing the burden on an individual and leading to increasingly taxing demands on coping strategies (59).

The second heuristic concerns situating biological development within an environmental context, sometimes called "biological embedding". This reflects an interest in how social contexts "get under the skin" to change biological processes. It is clear that epigenetic changes represent one such possibility (54). Other candidate mechanisms include changes in the neuroendocrine system (53) and altered neural processing of social cues (60-63).

Integrating research about the neurobiology of learning may prove to be a powerful way to test novel hypotheses about how the environment comes to regulate behavior. This is because successful social adaptation reflects children's ability to learn from complex and varied interpersonal experiences. Children need to discern factors including cues for approach versus withdrawal, actions that lead to punishments versus rewards, and which behaviors lead to success in having needs and desires met. These processes become increasingly intricate and fine-tuned as relevant neuroanatomical systems develop, and as the range, complexity and amount of social information increases for the developing child.

A focus on developmental processes allows us to formulate questions about which neural mechanisms we use to process socio-emotional information, how these mechanisms are themselves shaped by social context, why adverse social environments confer risk for children, and, perhaps, what sorts of neutrally informed interventions might remediate deficits in self-regulation.

Issues for future directions

A number of issues are likely to be the focus of increased interest in the near future. First, it is not yet clear whether it

is most fruitful to focus on specific stressors (such as parent psychopathology or physical abuse), or if a broader conceptualization of the effects of stress on children's development is sufficient (37). For example, Hanson et al (64) found that infants from very low-income families had lower volumes of gray matter, a tissue critical for processing of information and execution of actions. Differences in brain growth were found to vary with socioeconomic status, with children from lower-income households having slower trajectories of growth during infancy and early childhood. These volumetric differences were associated with the emergence of disruptive behavioral problems (64).

Similar cognitive and neurobiological differences have been reported in children who experienced early neglect, especially children raised in institutionalized settings (65, 66). For example, children who suffered early neglect showed developmental deficits in prefrontal white matter microstructure, consistent with more diffuse organization, and this was related to neurocognitive deficits (67). Thus, a broad range of stressful early life experiences may be associated with similar developmental responses.

Another challenge is how to conceptualize stress in children. We do not yet fully understand when stress exposure will be developmentally inconsequential versus harmful. The next wave of research in the field of developmental psychopathology will need to address questions about what kinds of circumstances are necessary for environmental experience to sustain a long-term impact on behavior. We need to better understand thresholds for when issues such as stress move from tolerable to toxic, and to identify the central differences between individual's responses to adversity. Such questions are in the service of leveraging this understanding into treatments that are effective and appropriate for individuals at different phases of development.

Clinical implications

An elucidation of developmental processes includes understanding adaptation as well as maladaptation. Therefore, a key aspect of developmentally appropriate interventions requires contextualizing a child's behavior in terms of how it may have been useful to the child in the past. It appears that some cognitive, affective and behavioral patterns that emerge in stress-exposed children may have allowed these children to cope with aberrant life circumstances. As an example, in a psychiatric context, we construe anxiety as a disadvantage. Indeed, anxiety is problematic for individuals living in low-danger, highly consistent environments. But if danger or uncertainty is high, then keeping a low profile and responding quickly to possible threat may be useful. For this reason, it is important to view symptoms within the child's life context rather than solely within their present circumstances. If a child is continuing to live in a family context that is unstable, where threat is high, it may well be harmful to reduce the child's anxiety or vigilance to threat. Even at

high cost, children need the supports to cope with the realities of their lives.

As clinicians and researchers begin to develop new and effective treatments for children, a challenge will involve learning how to tailor interventions for given individuals based on those individuals' specific biological and environmental circumstances. At present, many treatments for children remain somewhat generic, with popular approaches such as cognitive behavioral, mindfulness or attachment-oriented therapies being applied similarly across a range of mental health conditions, ages and individual differences. In addition, intervention studies tend to focus on very broad, non-specific behavioral outcome measures, such as ratings or interviews of overt symptomatology, school achievement, or observed ratings of behavior. But our behavioral constructs have not yet evolved to have the same level of mechanistic specificity as newer biological measures. More sensitive and specific behavioral measures will be necessary to truly discern the processes underlying mental health issues.

There is hope for effective interventions. Although data suggest that social experiences can alter human physiology, these changes are not necessarily permanent. For example, there is some evidence for epigenetic reversibility from rodents within the glucocorticoid receptor system (68). Such advances will require not only that we discover ways to target and change biobehavioral processes, but that we are able to personalize treatments based on the nature and timing of a child's experience and the individual child's sensitivity/reactivity to those experiences.

If the hypothesis is true that the early life experiences believed to precipitate psychological problems for young people also undermine their lifelong physical health, this would imply that the burden of adult and late-life diseases could also be reduced by successfully improving the psychological health of children. This will be the challenge for the next decade of developmental psychopathology.

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