1 Capturing the Dynamic Endophenotype

A Developmental Psychophysiological Manifesto

Sidney J. Segalowitz and Louis A. Schmidt

WHY SHOULD DEVELOPMENTALISTS BE PARTICULARLY INTERESTED IN PSYCHOPHYSIOLOGY?

Whether we like it or not, those of us interested in psychological development can never get very far away from some form of the nature-nurture question. In general, we have become more careful about ascribing complex behavioral attributes to purely biological substrates or solely to different life experiences. However, often this care is a reflex designed to avoid arguments and not due to true insights. Yet in order to be inclusive, developmental psychologists usually now acknowledge some sources from each, a kind of nature-plus-nurture approach. Some developmental disabilities, however, have often been talked about (depending on the background of the speaker) in terms of either nature or nurture, although most people today would point to both factors. One example is developmental dyslexia, which was originally postulated to have a biological familial basis (Orton, 1937), with various models of cortical insufficiency being blamed (see Pennington 2002, for a review). These insufficiencies include a series of cortical regions noted for their anatomical relation to reading (e.g., inferior parietal lobule), functional modules related to the reading process (e.g., phonological awareness), or sometimes both, such as a model of dyslexia focusing on an anatomically underdeveloped magnocellular system leading to functional deficits that might account for reading difficulties (Stein & Walsh, 1997). Some have suggested polygenic models through twin studies and single gene etiologies through linkage studies (Ingalls & Goldstein, 1999; Meng et al., 2005). At the same time, however, there have been those who discuss poor reading in the context of poor instruction within an awkward writing system (such as English), suggesting that the problem is not one of decoding abilities but

rather one of the teaching method used to link meaning to written forms (e.g., Goodman, 1973; Smith, 1977).

Another approach to the issue of nature-plus-nurture is to focus on statistical interactions of independent biological and experiential factors. An example is the developmental psychology of social/personality traits such as shyness in typical development. Evidence suggests that temperamental shyness is driven by a biological system that has various genetic and structural correlates (see Fox et al., 2001, 2005; Kagan, 1994; Schmidt & Schulkin, 1999, for reviews). Others, however, have argued from a more environmental etiology of childhood shyness linked to early attachment between mother and child (e.g., Stevenson-Hinde, 2000).

Perhaps the strongest advocate of a biological predisposition (i.e., nature) to childhood shyness is that of Kagan and his colleagues. Kagan and Snidman (1991) found that a small percentage of typically developing children (between 5 – 10%) who exhibited extreme fear and wariness in response to novelty during the first years of post-natal life were likely to be behaviorally inhibited and shy during the preschool and early school age years. These temperamentally shy children were likely to possess the short allele of the serotonin transporter (5-HTT) gene (Fox et al., 2005) and are characterized by a distinct pattern of central, autonomic, and adrenocortical activity during baseline conditions and in response to social stress (see Schmidt & Schulkin, 1999, for a review). For example, temperamentally shy children are known to exhibit greater relative right frontal EEG activity, high and stable heart rate at rest (Fox et al., 2001; Kagan et al., 1987, 1988), and high morning basal cortisol levels (Kagan et al., 1987, 1988; Schmidt et al., 1997). These patterns of psychophysiological and neuroendocrine responses are also heightened during social stress (Schmidt et al., 1999). However, only a subset of temperamentally shy children who possess these psychophysiological and neuroendocrine responses actually go on to develop shyness and social problems, suggesting that experience and context (i.e., nurture) may also be critical.

Fox and his colleagues (2005) found that among the children who possessed the short (versus long) allele of the 5-HTT gene, only those whose mothers perceived themselves low in social support actually turned out to be shy. The children with mothers who perceived themselves high in social support were less likely to be shy and behaviourally inhibited. Accordingly, the interaction of biology and context provides us with a better picture of developmental outcome (e.g., who will develop shyness).

Another recent example of typically developing shy children from our laboratory illustrates the need to examine functional interactions in human developmental science (Brunet, Mondloch, & Schmidt, 2006). Endogenously driven temperamental shyness may set up a situation in the child whereby

experience may be altered, which in turn may alter the functional capacity of neural networks. For example, we noted that temperamentally shy children (nature may have wired them differently) may alter their experiences with faces such that they exhibit deficits in some aspects of face recognition. These deficits are for a specific type of face recognition known as second-order or spacing among features. Temperamentally shy children exhibit deficits in their ability to process spacing among features in faces, a pattern of deficit also observed in children who had early visual deprivation due to congenital cataract. This deficit resulting from the lack of experiences with faces may set in motion a cascade of secondary negative effects such as multiple social problems that are often observed in some shy children due to their inability to perceive accurately others' facial emotions. Thus, the dispositional feature (i.e., temperamental shyness) or main effect reveals only so much about the temperamentally shy child. Both the child and the developmental context or experience need to be considered to provide a picture of the mechanisms involved in the development of shyness.

These examples from atypical and typical development serve to illustrate that both biological and experiential factors are intrinsic to the development of skills and traits. However, current research requires more integration, and our thesis is that psychophysiology is well placed to be in the center of this integration.

WHY IS PSYCHOLOGICAL DEVELOPMENT FUNDAMENTALLY CONSTRUCTIVIST?

We think it is fair to say that developmental psychology as a field has become essentially constructivist in Piaget's (1971) sense, with the debates only focusing on the details. Most of us now see children as being highly active in the construction of their own minds, as opposed to being the passive recipients of mental structures, whether the transmission is through a genetic "blueprint" or through environmental shaping. This constructivist approach has won the day, the fundamental argument being that the child is an active player in the development of his or her own mental structures. We accept this constructivist model for reasons that go well beyond anything Piaget wrote or knew about. We now know that the constructivist model appears to be the most robust, fitting both the known facts about brain growth and about mental development. There is more than a little irony here, given that Piaget had given up on brain growth as being part of the story of psychological development (see Segalowitz, 2007, for an outline of the historical issues). We now know that the growth of neural networks is heavily dependent on prespecified growth tendencies but is sculpted by experience twice. The first

time is evidenced in the role of active attention and stimulation on cortical growth; dendritic growth and synaptic proliferation are fed at least to some extent by mental activity (Diamond, 1988; Kandel, Jessell, & Sanes, 2000). The second time involves the sculpting of those networks. Considerable evidence exists that this process starts within the sensory systems very soon after birth, such as when visual experience alters the balance of connections within the visual system (Kandel et al., 2000). As far as we know, this process is the pattern for other sensory modalities and multimodal functional systems as well, such as those subserving language, spatial thinking, music, and so on. Furthermore, lack of input within one modality can dramatically alter the way the sensory systems are connected. For example, we find that in congenitally deaf or blind individuals, the linkage between sense organs and cortex is affected by deafness and blindness (Fieger et al., 2006; Stevens & Weaver, 2005). What appears to be the normal pattern of cortical networking is dependent on experience setting the stage for the unfolding of the neural plan. Such influences from experience are not confined to very early stages of development; the brain's structural and functional connections are affected by musical experience several years after birth (Elbert et al., 1995; Fujioka et al., 2006).

But all these patterns only make sense when we understand the interactions between the main effects of biological factors (genes, nutrition, prenatal, chemical, and health environment) and experience (sensory function, cognitive processes including attention and memory, social functions such as emotional interchange and communication, parenting, peers, extra-familial non-normative events, abuse, etc.). In concrete terms, development can only be understood as the growth response of the organism's particular biochemical and structural characteristics within contexts that relate to the instructions in those characteristics. The biochemical instructions built into the biological system are interpreted within the particular context in which they are found, something that has been understood in embryology for over a century and a half, but only appreciated more recently within developmental psychology. This process is also known by another meaning of the term "interaction."

WHAT IS THE MEANING OF INTERACTION?

The term interaction has come to take on more than one meaning within the developmental context, but two in particular concern us here. The first is the statistical meaning: An interaction of independent factors involves matching biological characteristics (e.g., genetic) with experiences (i.e., G × E). A classic example is the genetic combination that puts a child at risk for

phenylketonuria (PKU). PKU only produces a negative outcome when a diet supplies phenylalanine. Because all natural diets produce a negative outcome, PKU appears to be a main effect "genetic" disease. However, the genotype presents a (highly likely) predisposition that then unfolds in standard environments. This example is one of the only instances for which we have virtually all the details. Another example, increasingly more common now that we have the appropriate technology for genetic typing, is when children who possessed the short versus long allele of the 5-HHT gene were compared on levels of shyness at age four years. The main effect for genotype was not significant (Schmidt et al., 2002). However, when we considered perceived social support of mothers in relation to the children's short versus long allele of the 5-HTT gene, we found a significant interaction on childhood shyness (Fox et al., 2005). Children with the short allele who had mothers low in perceived social support were likely to be more behaviorally inhibited and shy at age seven years than children either with the long allele of the 5-HTT gene or with mothers high in perceived social support.

Another complex interaction, and for which we are starting to understand the mechanisms, is illustrated by the example of how a gene that regulates the activity level of monoamine oxidase A (MAOA), which is critical for metabolizing catecholamine neurotransmitters, interacts with early stressful experiences to put the person at increased risk for antisocial behavior (Caspi et al., 2002). Now that DNA typing is possible, similar interactions are being discovered, including those for the serotonin transporter associated with affective disorders (Caspi et al., 2003; Hariri et al., 2005) and catechol-o-methyl transferase (COMT), another dopamine transporter gene, associated with a predisposition for schizophrenia (Weinberger et al., 2001). Despite these very important advances in understanding G × E interactions that influence brain function and outcome, these interactions cloud the mechanism of a different interpretation of the term "interaction."

The second meaning for the term interaction goes beyond just the genes *per se* and focuses on their function. The presence of the genes is not really the issue. It is the polypeptide mappings of the genes that are important, because these mappings lead to the chemical structures that influence the brain's structures and functions. The genetic activations that map onto these polypeptides are necessarily influenced by experience, acting through the circulating hormones. The fundamental aspect of interest then is the outcome of the genes' activation. This interaction is derived from what is called the gene-environment interplay (Rutter, Moffitt, & Caspi, 2006). Just as the child's social behavior can be mapped by following the child-parent dynamic, the child's growth of brain function can be best understood through the dynamic

between biological underpinnings and experience. This dynamic helps guide the functional growth of the brain and accounts for the G × E interaction through the G × E interplay; genes influence the growth and activity of cells as a function of the context. This notion was first discovered functionally through careful observation of mother-pup social interactions that led to sex-stereotyped behavior in rats, and this effect was documented without knowledge of underlying genetic mechanisms (Moore, 1992). We now know from the seminal work of Michael Meaney and Moshe Szyf that the mechanism is one that facilitates or restricts the genome from realizing its potential options (Meaney & Szyf, 2005).

Thus, main effects themselves are interesting initial guides, but they do not really explain the variance of interest to developmental psychologists (except for the obvious outcomes that need more action than clever research, e.g., starvation is bad for everyone, light is needed for visual development, and so on). In contrast, statistical interactions point us in the appropriate direction; they imply the nature of the dynamic that explains development. However, the dynamic that this interaction implies is not at the level of the gene or environment as measured in the study; rather, it implies that the environment acts on the genome to regulate its activity in such a way that the neurodevelopmental pathway is altered. The interaction is the guide to the gene-experience interplay: interplay is the crucial component. Accordingly, the main effect of genes does not add to our understanding of developmental processes; it is the interplay (resulting in interactions) that clarifies development.

This interplay leads us to examine partial outcomes at a middle level, and the most interesting predictors that add to developmental theory are these middle-level dynamic outcomes from the genotype-environment interplay. No matter what the genetic or environmental pressures or their combination which may push the brain to be the way it is, we need to measure the state of central nervous system activity. This middle level state reflects the outcome of the G × E interplay, and the only way to examine this level in practical terms for most developmental psychologists is with psychophysiological methods. For example, researchers have hypothesized that inhibitory control networks involving various structures of the prefrontal cortex are needed to understand attention deficit hyperactivity disorder (ADHD), the development of behavioral and emotional self-regulation, and so on. This middle level of brain function is sometimes referred to as endophenotypes in order to capture the sense that they are both developmental outcomes and predictors of behavior (Castellanos & Tannock, 2002). We may also refer to them as neuropsychological and psychophysiological constructs. The study of the middle level permeates neuropsychology, with applications to

psychopathology (e.g., Savitz, Solms, & Ramesar, 2005), impulsivity (Congdon & Canli, 2005), and even alcoholism (Hesselbrock et al., 2001). However, in using this middle level to understand syndromes, we must be careful not to exaggerate the explanatory value of the isolated endophenotype. For example, although those at risk for alcoholism have often been shown to have a reduction in P300 amplitude, this is not a specific marker and must be only part of the full endophenotype (Hesselbrook et al., 2001). The hope is that this neurophysiological level will help us bridge the gap between genotype and experience that will help clarify their interplay (Gottesman & Gould, 2003).

In order to bridge this gap, we may need to treat our psychophysiological measures as both predictors and outcomes, something that happens routinely in developmental psychophysiology. For example, consider the psychophysiological construct of frontal EEG asymmetry. Greater right frontal EEG activation has been used as a predictor of vulnerability to anxiety (see Davidson, 2000), and it has also been treated as a developmental outcome, reflecting the risk in emotional development for infants of depressed mothers (Field, Fox, Pickens, & Nawrocki, 2005). It would be consistent to find that the frontal EEG asymmetry is more likely in certain genotypes. In other words, psychophysiological measures reflecting this middle level may be efficient mediators between predisposition (genetic or otherwise) and outcome.

Thus, the importance of these endophenotypes for developmental psychology cannot be overstated: *It is our task as developmental psychologists to further our understanding of the dynamics of development through the interplay of function and structure, and this level of analysis must be our focus.*

HOW CAN WE MEASURE THIS ENDOPHENOTYPE LEVEL OF FUNCTION AND STRUCTURE?

Purely behavioral measures are no longer considered adequate. There was a time when most developmentalists employed only behavioral measures. Thus, researchers used complex problem-solving tasks such as the Wisconsin Card Sorting Task (WCST) or Tower of London (TOL) in order to tap into the "health" or "growth" of the prefrontal cortex (PFC). Similarly, a researcher might infer a hemisphere activation bias from a dichotic listening or a visual half-field task involving the detection or categorization of emotion. However, we now know this approach is wrong for two basic reasons. First, none of these tasks are process pure and reflect many brain functions and structures. Therefore, we cannot expect that they reflect activity of a single brain network. Second, children do not solve complex problems the same way as do the clinical adults on whom the tasks were standardized in the first place. Thus, we

do not know which brain networks are reflected in good or poor performance in children.

In contrast to just one or two decades ago, the methods of choice for getting at this middle level are now available to developmental psychologists. What we need are measures that reflect the activation of specific neural systems within the context of specific tasks designed to test our hypotheses. Brain imaging systems provide some of these measures. For example, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) allow challenges to be presented to the participant while the brain is scanned for regions of specific activation. Although fMRI has some obvious benefits in its spatial resolution, the technology has some serious limitations, whether the paradigms used are event-related fMRI or blocked trials. First, fMRI is very expensive and therefore few labs can afford multiple studies with the large sample sizes needed to look for joint developmental and gender effects (not to mention the inclusion of personality or cognitive characteristics as well). Second, the demands of the machinery are relatively intrusive, making it not very friendly to young children. Third, the technology requires very limited movement and actions, in turn limiting the contexts and tasks available for use with children. Fourth, serious interpretive problems exist, owing to the nature of the non-additive factors designs typically employed (i.e., the appropriate baseline is not always clear). fMRI is one technology that requires a baseline subtraction in order to interpret individual or group differences, and it is not always clear how to go about doing this when developmental groups may differ on the baseline condition. PET is even more limited in flexibility of paradigms and is more invasive than fMRI, making it inappropriate for normative developmental studies.

The mainstays of psychophysiology are fully appropriate for the middle level of analysis: electroencephalogram (EEG), event-related potentials (ERP), electrodermal activitiy (EDA), electromyographic (EMG), and electrocardiogram (ECG) analyses all have adequate temporal resolution for studying behaviors that at least approach normal functions. They are also relatively inexpensive, are comparatively non-invasive, and can be applied to children of all ages in basic and applied or clinical research settings, as long as the children are reasonably cooperative. The methods for spatial resolution of brain function are improving for EEG and ERPs, but they probably will never achieve that of fMRI or PET. However, EEG and ERPs are increasingly interpreted as reflecting systems rather than regions of activation. Even in cases where the generator of the component seems to be well established, such as the error-related negativity associated with generators in the dorsal anterior cingulate cortex, it is also understood that this brain area is simply part of

a larger network complex including other major structures in the prefrontal cortex (Devinsky, Morrell, & Vogt, 1995). These measurements are made in the order of hundredths or thousandths of a second; EEG and ERPs capture these temporal dynamics that imaging techniques cannot. Some newer technologies such as magnetoencephalography (MEG) and event-related optical signal (EROS) are promising, although they have their own limitations, especially for activity reflecting deep brain structures.

Some wide-ranging functional systems are not easily located to a single region within the nervous system. These indirect measures of brain activity include non-invasive techniques relating to heart rate and its variability, as well as to cardiac vagal tone. Still another class of structures (e.g., HPA axis, frontal cortex, and forebrain areas) is tapped by examining hormones related to the stress system (e.g., cortisol) that can be collected non-invasively in saliva.

SUMMARY AND CONCLUSIONS

Research questions in developmental psychology always come back to the nature-nurture question, but they are now better characterized as structural versus adaptational issues. In the past few years, we have grown to appreciate the middle level for its explanatory power. A middle level approach is sensitive to both structural and functional aspects of the system. This middle level is best reflected in psychophysiological measures that can measure ongoing dynamic changes in real time. These measures reflect the system's outcome of this nature-nurture interplay and can be used non-invasively with pediatric populations.

ACKNOWLEDGMENTS

The writing of this chapter was funded in part by grants from the Natural Sciences and Engineering Research Council (NSERC) of Canada awarded to SJS and the Social Sciences and Humanities Research Council (SSHRC) of Canada awarded to LAS.

References

Brunet, P. M., Mondloch, C., & Schmidt, L. A. (2006). *Shy children show deficits in some aspects of face recognition.* Manuscript submitted for publication.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., Taylor, A., & Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 29*, 851–854.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Neuroscience Reviews, 3*, 617–628.

Congdon, E., & Canli, T. (2005). The endophenotype of impulsivity: Reaching consilience through behavioral, genetic, and neuroimaging approaches. *Behavioral and Cognitive Neuroscience Reviews, 4*, 262–281.

Davidson, R. J. (2000). Affective style, psychopathology, and resilience: Brain mechanisms and plasticity. *American Psychologist, 55*, 1196–1214.

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behavior. *Brain, 118*, 279–306.

Diamond, M. C. (1988). *Enriching heredity: The impact of the environment on the anatomy of the brain.* New York: The Free Press.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., & Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science, 270*, 305–307.

Fieger, A., Roder, B., Teder-Salejarvi, W., Hillyard, S. A., & Neville, H. J. (2006). Auditory spatial tuning in late-onset blindness in humans. *Journal of Cognitive Neuroscience, 18*, 149–157.

Field, T., Fox, N. A., Pickens, J., & Nawrocki, T. (1995). Relative right frontal EEG activation in 3- to 6-month-old infants of "depressed" mothers. *Developmental Psychology, 31*, 358–363.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21.

Fox, N. A., Nichols, K. E., Henderson, H., Rubin, K., Schmidt, L. A., Hamer, D., Pine, D., & Ernst, M. (2005). Evidence for a gene-environment interaction in predicting behavioral inhibition in middle childhood. *Psychological Science, 16*, 921–926.

Fujioka, T., Ross, B., Kakigi, R., Pantev, C., & Trainor, L. J. (2006). One year of musical training affects development of auditory cortical-evoked fields in young children. *Brain, 129*(Part 10), 2593–2608.

Goodman, K. S. (1973). The 13th easy way to make learning to read difficult: A reaction to Gleitman and Rozin. *Reading Research Quarterly, 8*, 484–493.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry, 160*, 636–645.

Hariri, A. R., Drabant, E. M., Munoz, K. E., Kolachana, B. S., Mattay, V. S., Egan, M. F., & Weinberger, D. R. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry, 62*, 146–152.

Hesselbrock, V., Begleiter, H., Porjesz, B., O'Connor, S., & Bauer, L. (2001). P300 event-related potential amplitude as an endophenotype of alcoholism: Evidence from the collaborative study on the genetics of alcoholism. *Journal of Biomedical Sciences, 8*, 77–82.