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Skating to where the puck will be: The importance of neuroimaging literacy in child psychiatry

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Asked to explain the secret to his success, the pre-eminent hockey player Wayne Gretzky asserted that he skated to where the puck would be, rather than to where it was. If “the puck” in this instance is pathophysiologic knowledge about pediatric psychiatric illnesses, then “skating to where the puck will be” leads us directly to the brain. Of note, this focus on the brain does not obviate an equally strong focus on the environment: data suggest that associations between environmental influences and risk for psychopathology reflect the impact of such influences on brain development.¹ Thus, if child psychiatrists are to approach patient care with state-of-the-art knowledge about psychopathology, it is important that they be knowledgeable about brain structure and function. In order to do that, they must be educated consumers of the emerging neuroimaging literature.

Why is neuroimaging literacy important for practicing psychiatrists? Put another way, how are neuroimaging techniques moving the field forward? As noted by several authors in this issue, such techniques make it possible to link the study of behavior, psychiatrists’ stock-in-trade, with studies of the brain. As brain-behavior connections are elucidated, new treatment approaches can be developed, since both pharmacologic and psychotherapeutic interventions can potentially target any one of a number of links in the brain-behavior chain. In addition, each one of these brain-behavior “links” is a potential biomarker that, sometimes in combination with genetic markers, might facilitate diagnosis, index risk, and/or be used to monitor treatment response. Finally, in some instances, as for example in anxiety disorders, human neuroimaging studies build on a wealth of data in animal models delineating relevant neural circuitry, making it possible for psychiatric practice to be advanced by the recent revolution in neuroscience. Examples of each of these applications of neuroimaging techniques can be found in this issue of the *Journal*.

Clearly, neuroimaging is playing an increasingly central role in psychiatric research. Nonetheless, it is important to emphasize that these are early days: the brain and brain illnesses are remarkably complex, our corpus of neuroimaging data is still limited, and the technology, while developing rapidly, is still relatively new. It will be years, if not decades, before neuroimaging can contribute meaningfully to the diagnostic process; even when it does, neuroimaging will be used as a complement to, not a substitute for, expert clinical assessment. While diagnostic applications of imaging may be years away, we will highlight below areas where neuroimaging already has provided clues regarding promising new treatment approaches. Thus, it is clear where the puck is headed, and clear that neuroimaging will play

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an important role in research---research that will ultimately impact on practice---for years to come.

For all these reasons, we (the *Journal's* editorial team) view fostering neuroimaging literacy in the child psychiatry community as an important goal. Admittedly, this is not easy: even for researchers in the field, neuroimaging papers can be confusing, tedious to read and (dare we say it?) boring. So we focused first on our editorial efforts, encouraging authors and reviewers to place a high priority on clear communication and assisting them in doing so. Then, in March 2008 we launched *Applied Brain Imaging*, a column edited by Drs. Andrew Gerber and Bradley Peterson that is designed to, over time, acquaint our readers with imaging technologies important in child psychiatry (specifically, structural and functional magnetic resonance imaging (sMRI and fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), event related potentials (ERP), and magnetoencephalography (MEG)). Initial columns in this series focused on "What is an Image?"² and on sMRI³.

This month's special section represents our latest effort toward updating our readership about advances in neuroimaging. At the 2007 AACAP meeting in Boston, Drs. Daniel Pine and Bradley Peterson organized a Research Forum entitled "The Future of Neuroimaging: Relevance for Psychiatry." Given the enthusiastic interest generated by the Forum, we invited presenters to submit manuscripts for publication, and were happy to receive four: Marsh, Gerber, and Peterson reviewing normal brain development⁴; Nelson and McCleery on using ERPs to study normal and abnormal development⁵; McMaster, O'Neill and Rosenberg reviewing neuroimaging findings in pediatric obsessive compulsive disorder (OCD)⁶; and Pavuluri and Sweeney on using behavioral testing, in combination with fMRI, to understand brain mechanisms mediating bipolar disorder (BD), attention deficit hyperactivity disorder (ADHD), and other childhood psychopathology.⁷ While these manuscripts were wending their way through the peer review process, we were fortunate to accept four additional neuroimaging manuscripts: Pfeifer et al reporting a meta-analysis of amygdala volume in pediatric BD⁸; Garrett et al studying neuroanatomical abnormalities in late adolescents with familial ADHD⁹; Janssen et al testing whether sMRI data, obtained at the onset of first-episode psychosis (FEP), can be used to predict diagnosis one year later¹⁰; and Pauley et al using fMRI to study emotion-cognition interactions in adolescent schizophrenia.¹¹ These eight papers, plus an *Applied Brain Imaging* column by Pine, Leibenluft, and Guyer on fMRI studies in adolescent anxiety disorders¹², round out this month's special section on neuroimaging. We hope that you will enjoy your first read-through, but we also anticipate that you will want to hold on to this issue of the *Journal* and come back to it (and the forthcoming installments of *Applied Brain Imaging*). Like fine wines, neuroimaging papers often warrant savoring.

Marsh, Gerber, and Peterson's paper on normal development is an important starting place.

⁴ For psychiatrists to understand disease as it manifests in the developing brain, we must first understand normal brain development, since psychopathology can only be defined in contrast to normative development. sMRI and the emerging technology of DTI, the latter used to study the structure of white matter tracts, play a special role in studies of normal development because they can be used beginning *in utero*. The authors describe how sMRI and DTI studies can document the impact of synaptogenesis, myelination, apoptosis and synaptic pruning on brain structure. These processes begin *in utero* and continue, in the case of myelination at least, until adulthood. Maturation occurs earliest in sensory areas, followed by motor and then association cortex, with posterior regions generally maturing before anterior ones. Cross-sectional and, more recently, longitudinal studies of normal brain development, coupled with studies in patient populations, suggest that schizophrenia may be characterized by excessive synaptic pruning,¹³ while ADHD may be characterized by a delay in such pruning.¹⁴ DTI studies document white matter tract development through childhood, particularly in frontal and striatal regions, and suggest that youth with autism spectrum disorders (ASDs) may experience early

maturation of frontal white matter.¹⁵ Finally, fMRI studies of important cognitive and emotional processes across normal development are also relevant to psychiatric illness. For example, inhibitory function, the maturation of which appears to entail increased engagement of fronto-striatal circuitry (e.g., 16), is impaired in several illnesses, including ADHD, Tourette's, OCD, and BD.

Next, as Nelson and McCleery note in their review,⁵ ERPs are a particularly interesting neuroimaging modality in child psychiatry because this technique can be used from infancy on up. While ERPs resemble sMRI and DTI in being applicable to very young children, ERPs are an important complement to these other two modalities because ERPs are low cost, particularly well tolerated, and measure brain function, as opposed to structure. Specifically, ERPs record the brain's electrical activity in response to a stimulus. Further, compared to other functional neuroimaging techniques such as fMRI, ERPs (and their technological descendent, MEG) have particularly fine temporal resolution, on the order of milliseconds, which can facilitate investigators' efforts to deconstruct complex psychological processes into their component parts.

Nelson and McCleery describe ERP studies of sensory processing, face processing, and memory and attention in infants and very young children. For example, using ERPs, it has been demonstrated that preschoolers exhibit the same face-sensitive neural responsiveness as do adults, specifically, the N170, a negative deflection measured over the occipital-temporal cortex that peaks 170 msec after the stimulus, and shows a larger and faster response to faces than to other pictorial stimuli.¹⁷ In infants, two other ERP components, the P400 and N290, also show face sensitivity and may thus be developmental precursors to the N170.¹⁸ Using ERPs, it is possible to identify differences in normal infants' neural responses to happy vs. fearful, and familiar vs. unfamiliar faces, and to identify interindividual differences in these measures, for example when comparing institutionalized, neglected infants, or preschoolers with ASDs, to age-matched controls (19, 20). In this way, objective data obtained using ERPs might ultimately be used to complement clinical observations of developmental delays in social cognition.

Focusing on pediatric OCD, McMaster, O'Neill and Rosenberg next demonstrate how neuroimaging findings can begin to inform treatment.⁶ sMRI and MRS studies, building on work in animal models, implicate the fronto-striatal-thalamic circuit in the pathophysiology of pediatric OCD. In particular, MRS studies, which yield information about neurochemical abnormalities in specific brain regions, indicate large differences between patients with OCD and controls in glutamate regulation in this circuit. Informed by genetic findings also implicating glutamatergic mechanisms in OCD, clinical trials of the glutamate modulator riluzole have been initiated.²¹

Coupled with examples from pediatric anxiety (see below), this work provides a harbinger of an important, and very promising, new development: investigators using information from neuroimaging studies as a bridge between basic work in animal models and molecular genetics, on the one hand, and studies designed to generate hypotheses on novel treatment approaches, on the other. Of course, the ultimate test of efficacy will emerge from randomized controlled trials. However, as this example demonstrates, by linking basic science approaches with research in patients, imaging provides psychiatry with a new strategy for treatment development.

The final paper from the 2007 Research Forum is that by Pavuluri and Sweeney.⁷ Here, the focus is on fMRI as a tool to study brain-behavior associations in psychopathology, and this article shares many themes with Pine, Leibenluft, and Guyer,¹² this month's *Applied Brain Imaging* column. Pavuluri and Sweeney focus on applications of fMRI to pediatric BD and

ADHD, while Pine, Leibenluft, and Guyer focus on pediatric anxiety, but both papers describe how, using carefully designed behavioral tasks and fMRI, investigators can study the neural mechanisms mediating disease. An important take-home message is this: when reading an fMRI paper, focus on the task that subjects complete while being scanned. Authors should clarify for readers how brain-behavior associations, revealed by data obtained while patients and controls perform the task, can inform us about brain-behavior associations mediating patients' symptoms.

With examples from pediatric BD and anxiety, Pavuluri and Sweeney⁷ and Pine, Leibenluft, and Guyer¹² illustrate how fMRI studies using informative tasks implicate impaired "top-down" control of emotional and attentional processes in the pathophysiology of these illnesses. Specifically, deficient top-down control, in the form of impaired modulation of amygdala activity by the ventrolateral prefrontal cortex (a circuit whose function has been worked out precisely in animal models), is associated with anxious patients' tendency to attend to threatening stimuli, and with BD patients' tendency to attend to their emotional response, rather than to the task at hand. In the case of anxiety, such studies of brain-behavior-symptom associations suggest that teaching anxious patients to attend away from threat cues might have therapeutic effects, thus providing us with our second example of how neuroimaging can point the way toward novel treatments (the first being riluzole in pediatric OCD). As these examples demonstrate, it is likely that the "first fruits" of neuroimaging research, from the perspective of clinical practice, will be the development of new treatments based on insights gained from imaging data. Along similar lines, Pavuluri and Sweeney⁷ emphasize the importance of using fMRI to study patients before and after pharmacologic interventions. Such data can teach us about mechanisms mediating clinical response, while pointing the way toward more targeted treatments. Clearly, if child psychiatrists are to understand the neuroscience underlying new treatment options as they emerge, they must achieve neuroimaging literacy.

The four manuscripts rounding out this special issue complement these five reviews by providing specific examples of how neuroimaging can inform our understanding of childhood psychopathology. Pfeifer et al⁸, Garrett et al⁹, and Janssen et al¹⁰ each use sMRI to provide important developmental perspectives on, respectively, BD, ADHD, or early-onset first episode psychosis (FEP). Pfeifer et al⁸ report a meta-analysis of amygdala volume in pediatric and adult BD, finding evidence for decreased amygdala volume in pediatric, but not adult, BD. As the authors note, their findings suggest either that patients with BD and controls have different trajectories for amygdala development, or that early and late-onset BD have fundamentally different pathophysiologies. Garrett et al⁹, studying a relatively homogeneous sample of patients with ADHD (all had familial illness and were 15–19 years old), found larger right caudate and right inferior frontal gyrus volumes in patients vs. controls. This study contrasts with data suggesting decreased caudate volume in ADHD. To explain the disparity, these authors also adopt a developmental perspective, noting that other studies had wider age ranges, and suggesting that, as in BD, the developmental trajectories of brain development may differ between patients and controls.

Importantly, then, the question of whether patients, compared to controls, have increased, decreased, or similar volume in any brain structure may depend on when in the course of development a measurement is obtained. Like Garrett et al⁹, all but one of the studies comprising the meta-analysis of Pfeifer et al⁸ were cross-sectional, and all authors acknowledge the importance of longitudinal studies (such as those described by Marsh, Gerber, and Peterson⁴), while also noting the difficulty inherent in conducting such studies. Combining longitudinal and cross-sectional techniques, Janssen et al¹⁰ test whether sMRI data, obtained at the onset of FEP, can predict diagnosis a year later. Using discriminant function analysis, they found that both BD and schizophrenia were associated with decreased grey matter in the

left medial frontal cortex, while only schizophrenia was associated with such deficits in the left middle frontal gyrus.

Finally, Pauley et al¹¹ pick up a theme developed by Pavuluri and Sweeney⁷, namely, the utility of fMRI in studying interactions between cognition and emotion. In youth with schizophrenia, Pauley et al used a relatively novel emotion induction technique, aversive odors, to induce negative emotion in patients and controls. They then examined the impact of this intervention on brain activation while subjects performed an n-back working memory task, finding evidence of a dysfunctional thalamo-cortical network in schizophrenia.

These, then, are the contents of this special section on neuroimaging in this issue of the *Journal*. For psychiatrists, invested as we are in the “output” of the brain, i.e., emotion, cognition, and behavior, it can only be described as thrilling to be able to see the living brain at work. For those of us interested in childhood psychopathology in particular, it is fortunate that these powerful neuroimaging tools are noninvasive and, when used in appropriately supervised settings, extremely safe.

Granted, from the perspective of a practicing clinician, the promise of neuroimaging is still just that...a promise. Yet, as described above, we are already beginning to see how neuroimaging data can inform treatment development. Further, it is inevitable that, at some point, psychiatry will join other medical specialties in incorporating neuroimaging data into the diagnostic process. Thus, over time, the connections between what we know about the brain and what we do in the clinic will become tighter and tighter. As that process evolves, it is important that child psychiatrists develop neuroimaging literacy, so that they can understand those connections and use them to patients’ advantage. In other words, it is important that psychiatrists have the knowledge they need to be “where the puck is” when it arrives, so that they are able to receive it. We at the *Journal* promise to work hard to reach that goal, and to make the process of “skating” there as enjoyable as possible.

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