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# Imaging the "At-Risk" Brain: Future Directions



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**Abstract**

**Objectives:** Clinical neuroscience is increasingly turning to imaging the human brain for answers to a range of questions and challenges. To date, the majority of studies have focused on the neural basis of current psychiatric symptoms, which can facilitate the identification of neurobiological markers for diagnosis. However, the increasing availability and feasibility of using imaging modalities, such as diffusion imaging and resting-state fMRI, enable longitudinal mapping of brain development. This shift in the field is opening the possibility of identifying predictive markers of risk or prognosis, and also represents a critical missing element for efforts to promote personalized or individualized medicine in psychiatry (i.e., stratified psychiatry). **Methods:** The present work provides a selective review of potentially high-yield populations for longitudinal examination with MRI, based upon our understanding of risk from epidemiologic studies and initial MRI findings. **Results:** Our discussion is organized into three topic areas: (1) practical considerations for establishing temporal precedence in psychiatric research; (2) readiness of the field for conducting longitudinal MRI, particularly for neurodevelopmental questions; and (3) illustrations of high-yield populations and time windows for examination that can be used to rapidly generate meaningful and useful data. Particular emphasis is placed on the implementation of time-appropriate, developmentally informed longitudinal designs, capable of facilitating the identification of biomarkers predictive of risk and prognosis. **Conclusions:** Strategic longitudinal examination of the brain at-risk has the potential to bring the concepts of early intervention and prevention to psychiatry. (*JINS*, 2016, *22*, 164–179)

**Keywords:** Magnetic resonance imaging (MRI), Longitudinal examination, Prediction, Stratified psychiatry, Brain development, Population and time window

## INTRODUCTION

Biological psychiatry entails the study of how the brain functions to manage cognition, behavior, and emotion in health and disease. In recent years, magnetic resonance imaging (MRI) has emerged as a mainstream tool for developing models of brain structure and function. In large part, this shift toward MRI usage reflects the increasing ability of MRI techniques to non-invasively characterize inter-individual differences in the organization of human brain circuitry. Crucially, MRI measurements can be related to individual variations in cognition, behavior, and emotion. Already, MRI studies of clinical populations have offered several novel perspectives on pathologic processes. Perhaps most exciting, there is growing evidence that MRI may yield clinically useful brain-based biomarkers (Buckholtz & Meyer-Lindenberg, 2012; Castellanos, Di Martino, Craddock, Mehta, & Milham, 2013; Di Martino, Fair, et al., 2014; Kaiser, 2013; Kelly, Biswal, Craddock, Castellanos, & Milham, 2012; Watanabe, Kessler, Scott, Angstadt, & Sripada, 2014). To realize these ambitions, researchers are endeavoring to increase the validity and reproducibility of imaging findings via leveraging multicenter designs (Van Essen et al., 2013), as well as large-scale aggregate samples generated through data sharing initiatives (Di Martino, Yan, et al., 2014; Mennes, Biswal, Castellanos, & Milham, 2013; Nooner et al., 2012). However, increasing sample size alone will not be sufficient to address the broader range of neuroscientific and clinical questions, as most datasets collected to date are cross-sectional. While such datasets have value for efforts to differentiate populations from one another (e.g., establishing the neural correlates of illness,

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carrying out brain-based diagnostic classification), they are limited in their ability to support a mechanistic understanding of the developmental processes underlying psychiatric illness, as well as to offer predictions regarding risk or prognosis.

The importance and value of developing cohorts in which individuals are imaged repeatedly over the course of time (i.e., longitudinal designs) is reinforced by the growing consensus that most psychiatric illness is neurodevelopmental in origin. Some of the most compelling support for this notion are epidemiologic findings suggesting that at least 50% of mental disorders arise before age 14, and 75% before age 24 (Kessler, Avenevoli, & Merikangas, 2001). Furthermore, genetic research has documented the high heritability of many forms of severe psychiatric illness (e.g., autism, bipolar disorder, schizophrenia) (Burmeister, McInnis, & Zollner, 2008; Colvert et al., 2015; Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Muhle, Trentacoste, & Rapin, 2004). These findings are bolstered by the growing number of associations between psychiatric illness and genetic variants (i.e., common and rare) (Caspi & Moffitt, 2006; Gaugler et al., 2014; Martin, O'Donovan, Thapar, Langley, & Williams, 2015; Sandin et al., 2014), as well as undeniable familial associations with psychiatric illness (e.g., 19% risk for autism spectrum disorder [ASD] in younger siblings of an individual with ASD) (Ozonoff et al., 2011).

Arguably, the neurodevelopmental perspective of psychiatric illness suggests not only the need for longitudinal research, but also the need to begin research as early in development as possible. In support of these needs, imaging researchers are rapidly developing the capabilities needed for functional and structural imaging in prenatal and early postnatal life (e.g., neonatal imaging, infant imaging, toddler imaging) (e.g., Almli, Rivkin, McKinstry, & Brain Development Cooperative, 2007; Ramenghi et al., 2009; Reddy, Abuhamad, Levine, Saade, & Fetal Imaging Workshop Invited, 2014; Smyser, Snyder, & Neil, 2011). Undeniably, several technical challenges still exist, as exemplified by head motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Satterthwaite et al., 2013; Yan, Craddock, He, & Milham, 2013) and the various logistical hurdles of imaging during the prenatal period, or during natural sleep (Di Martino, Fair, et al., 2014). Nevertheless, pioneering studies have demonstrated the feasibility of longitudinally mapping developmental trajectories in clinical and non-clinical populations alike.

Beyond neuroscientific ambitions, the growing interest of the medical community in "personalized" health care and stratified (or "precision") interventions, is further motivating the generation of longitudinal datasets. In "stratified psychiatry" (Kapur, Phillips, & Insel, 2012), it is crucial to identify and validate objective measures or "stratifiers" capable of enhancing our ability to inform predictions of risk, prognosis, or treatment outcome, beyond that afforded by conventional diagnostic systems (e.g., DSM-5) or historical data. Such measures have the potential to guide clinical efforts focused on prevention, early intervention, and the selection of optimal treatments (Costa e Silva, 2013; Schumann et al., 2014). The genetics community has led the way in such pursuits, although marked gaps remain. While imaging has the potential to meaningfully contribute to these efforts, the prerequisite longitudinal data are yet to be generated.

Despite their potential benefits, the scale with which longitudinal studies can be deployed in imaging research remains limited by their associated costs and time-requirements. Realizing the need to balance promise with an appreciation of logistical challenges, it is our tenet that targeting high-yield "at-risk" clinical populations and age-ranges is essential for efficacious and impactful implementations of longitudinal imaging studies. As will be elucidated below, risk can be defined using a range of variables, including genetics, familial factors, fetal exposures, environmental exposures, and current psychiatric symptomatology. Our discussion is organized into four topic areas: (1) a special role of connectomics in psychiatric research; (2) practical considerations for establishing temporal precedence in psychiatric research; (3) readiness of the field for conducting longitudinal MRI, particularly for neurodevelopmental questions; and (4) illustrations of high-yield populations and time windows for examination that can be used to rapidly generate meaningful and useful data.

## A SPECIAL ROLE OF CONNECTOMICS

The principles and frameworks discussed in the present work are broadly applicable to various brain imaging methodologies. In recent years, the human connectome has taken a central focus in efforts to map brain function and structure (e.g., Van Essen et al., 2013). A growing number of studies are working to map changes in the connectome across the lifespan (Nooner et al., 2012), as well as to identify connectome-based markers of illness, risk and prognosis (see Castellanos et al., 2013 for review; Di Martino, Yan, et al., 2014). The increased focus on the connectome allows for more direct appreciation of interactions among brain regions, particularly between cortical and subcortical regions. Importantly, such complex interactions contribute to the occurrence of psychiatric illness, a concept originally espoused by Norman Geschwind in his 1965 papers entitled "*Disconnexion syndromes in animals and man*" (Geschwind, 1965a, 1965b). Recent advances in MRI imaging modalities are providing researchers with the critical tools needed for *in vivo* mapping of structural and functional brain connectivity underlying pathological symptoms. Although still in their infancy, studies of connectomes are rapidly extending models of psychiatric disorders, to integrate the concepts of hypo- and hyper-connectivity, as well as more complex disturbances embedded in the connectome (e.g., autism: Di Martino, Yan, et al., 2014; ADHD: Fair et al., 2010; schizophrenia: Whitfield-Gabrieli et al., 2009).

Given its role in psychiatry, there has been an increased interest in connectome-based analyses in individuals at risk of a disorder. Initial longitudinal efforts are emerging, a few of which will be introduced in this review. These efforts have capitalized on the increasing capabilities of diffusion imaging

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(Ameis & Catani, 2015; White, Nelson, & Lim, 2008), white matter volumetrics (Radua, Via, Catani, & Mataix-Cols, 2011), and resting-state fMRI (R-fMRI) (Castellanos et al., 2013) approaches. Looking forward, advances in quantitative MRI (see Alexander et al., 2011, for review), particularly relaxometry (e.g., myelin water fraction) and magnetization transfer (myelin volume fraction, axon volume fraction, g-ratio) methods, can provide researchers with tools capable of providing *in vivo* characterizations of myelin in healthy and disordered brains. In light of recent models suggesting the contributions of dysregulated myelination to early-life psychiatric disorders (Bartzokis, 2004), these quantitative MRI techniques, which focus on characterization of myelin properties (e.g., sheath thickness), are particularly important in imaging the "at-risk" brain.

## ESTABLISHING TEMPORAL PRECEDENCE

Optimally, the study of a given illness will lead to an understanding of its etiology and pathophysiological mechanisms; in turn, this information can be used to identify modifiable targets for intervention. For example, phenylketonuria (PKU) is an autosomal recessive disorder, for which the causal mechanisms, downstream effects, and the timing and optimal treatments are well understood. PKU is caused by mutations in the phenylalanine hydroxylase gene; the optimal intervention is to identify neonates soon after birth using a screening blood test and promptly begin a low phenylalanine diet. Such early identification and interventions work well for diseases with a clear etiology that can be validated through objective means such as a blood test. In contrast, the origins of most psychiatric disorders are poorly understood; they are presumed to be complex and the result of interactions between genetic and environmental factors over time, rather than a single causal factor occurring at a single time point.

Longitudinal designs can help address causality by demonstrating temporal precedence (i.e., "the cause" precedes "the effect"). Given the presumed multifactorial nature of psychiatric illness, imaging studies are unlikely to identify most etiologic agent(s) or processes. However, imaging can identify relationships between particular neurophenotypes (i.e., prototypic brain organizations) and later behavioral manifestations of illness. In some instances, a given neurophenotype can either indicate an increased risk for the later onset of a disorder or serve as a predictor of prognosis, without any assertions regarding causality. In either the risk or prognostic scenario, such information has the potential to guide clinicians' decision-making. As demonstrated in recent studies of depression (Liston et al., 2014; McGrath et al., 2014), researchers can attempt to explain variations in treatment response (i.e., responder *vs*. non-responders) based on neurophenotypic features assessed before treatment. Such distinctions are central to stratified medicine and can meaningfully impact clinical decision-making.

## RESEARCH READINESS OF LONGITUDINAL MRI

While few would argue against the potential scientific value of longitudinal MRI studies of the developing brain, the many logistical challenges and substantial expenses prompt concerns regarding the field's readiness to proceed. The recently awarded NIH Adolescent Brain Cognitive Development (ABCD) Study signals increased confidence in this regard. This effort is designed to determine the impact of substance use on the trajectories of brain, behavior, and cognitive development, while also identifying potential brain-based markers for risk. The cost of the proposed longitudinal examination of 10,000 nine-to-ten year old children over the next 10 years is projected to be US $300,000,000; its implementation will bring together more than a dozen imaging sites from around the United States and its success will depend on a combination of careful coordination and state-of-the-art neuroinformatics. Despite the welcomed endorsement of the imaging community's progress provided by the inception of the NIH ABCD Study, many questions remain as the community considers similar initiatives focused on other areas of psychiatry, or more technically challenging efforts focused on even earlier ages.

### Logistical Challenges Related to Imaging: Reliability and Validity

While longitudinal imaging studies to date have primarily used T1-weighted morphometry, a growing array of imaging modalities has been suggested (e.g., R-fMRI, diffusion weighted MRI, arterial spin labeling, quantitative T1/T2 mapping, and myelin water fraction (Deoni, Dean, Remer, Dirks, & O'Muircheartaigh, 2015; Dubois et al., 2014; Gao et al., 2015; Krogsrud et al., 2015; Sadeghi et al., 2013; Smyser et al., 2010; Walker et al., 2016; Wang et al., 2008). Given that scan session durations are limited by the tolerability of the scanner environment (particularly for developing and clinical populations) and cost ( ~$500–$700 per hr + manpower costs), investigators must determine which imaging modalities to include, and how to prioritize them, based upon readiness of these modalities for study at the present time. Central to assessments of the readiness for longitudinal examination are determinations of their reliability and validity of data collected for these imaging modalities (e.g., Finn et al., 2015; Jovicich et al., 2014; Kuhn et al., 2015; Mueller et al., 2015; Zuo et al., 2014). In particular, test–retest reliability is an essential prerequisite for longitudinal studies, as experimental error in measurements from one time point to the next inherently limits the detectability of meaningful time-related changes. Despite the best of intentions, hardware and software upgrades commonly occur during the conduct of studies; any such changes should be carefully denoted in datasets and considered at the analytic level when possible. Phantom measurements and comprehensive quality control assessments (NessAiver, NessAiver, Harms, & Xu, 2015) can be used to alleviate potential concerns related to these events.

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Although arguably less essential for single-site studies, inter-scanner reliability should also be considered for longitudinal examinations. It is generally accepted that the best solution to the maximization of inter-scanner reliability is standardization to a single scanner type and protocol (see Brain Genomics Superstruct Project, Holmes et al., 2015, for an example). However, efforts, such as the Pediatric Imaging, Neurocognition, and Genetics (PING) (Jernigan et al., 2015), have demonstrated it is possible to minimize protocol differences across scanner types (e.g., Siemens, GE, Philips). Additionally, a growing number of *post hoc* statistical correction approaches is becoming capable of minimizing the impact of scanner differences (Yan, Craddock, Zuo, Zang, & Milham, 2013). Importantly, for any multicenter design, it is critical to ensure that variables of interest do not vary across scanners (e.g., all ADHD participants imaged on scanner A but all typical comparisons on scanner B).

### Putting the Pieces Together from Fetus to Childhood

Enthusiasm has been building for imaging brain development from the fetus to childhood and beyond. However, we must acknowledge the challenges inherent to early life imaging methodologies. For example, the state of wakefulness during which children are scanned varies with age for task-independent functional MRI. With sufficient pre-scan habituation and training, children ages 5 years and older can usually cooperate with rest scans while awake. However, younger children (e.g., infants or toddlers) are unable to remain sufficiently still while awake, but can be scanned during natural sleep (see Di Martino, Fair, et al., 2014 for a review). While functional connectivity is known to vary systematically between awake and sleep states (Barttfeld et al., 2015; Fukunaga et al., 2006; Uehara et al., 2014), as well as between eyes-open and eyes-closed states (Wang, Li, Xu, & Ding, 2015; Zuo et al., 2014), it is not clear how these differences impact the reliability of intra- and inter-individual differences during a developmental time course. This is one of the challenging but important questions that can be addressed by longitudinal MRI studies.

### Non-imaging Logistical Challenges

Discussions of the readiness for large-scale longitudinal studies tend to focus most heavily on the reliability and validity of MRI measurements. However, it is equally important to take into account the behavioral, cognitive, psychiatric and physical characterizations to which MRI measures will be linked. Similar to the genetics community, imaging researchers are increasingly highlighting the need for "deep" (i.e., precise and comprehensive) phenotyping protocols (Loeffler et al., 2015; Rafii et al., 2015; Stepniak et al., 2014). Simultaneously, there is increasing pressure to obtain broader assessments, which provide a more holistic characterization of an individual (Nooner et al., 2012), although often at the cost of additional burden on participants and experimenters. Additional trends are an increased focus on the adoption of dimensional characterizations of behaviors and symptomatology, which can be used to transcend DSM-5 diagnostic classifications. A multitude of measurements are emerging for all of these domains, ranging from self-administered, clinician-administered, informant-based assessments, to more objective measures (e.g., device, computer, or laboratory measurements).

## SELECTION OF HIGH-YIELD TARGET POPULATIONS AND APPROPRIATE TIME WINDOWS FOR LONGITUDINAL EXAMINATION

How can we best design a longitudinal study? Should all longitudinal studies begin at birth, since many psychiatric disorders have early onsets and strong genetic influences? The answer may be "Yes" if a research question is etiological (i.e., causal links). However, from an implementation and timeliness perspective, this would likely be unrealistic and impractical for the vast majority of MRI studies. Critically, the ability of longitudinal MRI examinations to advance the stratified psychiatry agenda will depend upon (1) strategic identification of high-yield targets (e.g., risk populations), and (2) the selection of the appropriate time windows for examination. Here, we provide a targeted review of psychiatric imaging and epidemiologic studies that can help to build longitudinal MRI research models, with a particular focus on how to determine the appropriate time window(s) to answer specific research questions.

### Autistic Spectrum Disorder

ASD poses a range of challenges for the healthcare professions, which exemplify the complexities that can arise in the detection and treatment of neurodevelopmental disorders. The first challenge is the task of diagnosing autism. Beyond the core domains (i.e., social-communicative, repetitive and restricted interests/behaviors), ASD is characterized by marked clinical heterogeneity/comorbidity (Georgiades et al., 2013; Geschwind, 2009; Jeste & Geschwind, 2014; Matson & Williams, 2013; Wiggins, Robins, Adamson, Bakeman, & Henrich, 2012), which can lead to confusion and delays in diagnosis. The second challenge is the need to identify those most at risk for developing the disorder as early as possible, to create opportunities for early intervention. The third challenge is determining prognosis, which often cannot be determined until years after the initial diagnosis, except for the most severely affected cases. This is particularly critical for autism, for which long-term outcomes vary widely; some individuals experience substantial improvements as they mature, while others face significant, lifelong impairment, particularly those who are non-verbal (Bal, Kim, Cheong, & Lord, 2015; Pickles, Anderson, & Lord, 2014). It is the latter two challenges, focused on the establishment of risk and prognosis, which are best positioned to benefit from

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longitudinal research designs. Efforts aiming to improve the diagnostic process (e.g., identification of distinct neurophenotypic subtypes, identification of biomarkers of illness that can inform complex presentations) may also benefit from longitudinal data, although less directly.

### *MRI Predictors of Risk*

As with other neurodevelopmental disorders in psychiatry, researchers studying ASD are seeking a range of predictive biomarkers, capable of informing assessments of risk. Initial work with brain imaging suggests its potential utility in studying infants at risk (i.e., younger sibling of a child with ASD) (Elison et al., 2013; Wolff et al., 2015, 2012). ASD is highly heritable; for example, monozygotic twin concordance ranges between 0.77 and 0.99 (Colvert et al., 2015), and 18.7% of younger siblings develop ASD (Ozonoff et al., 2011). Appreciating the strong genetic contributions to ASD, longitudinal efforts have begun to scan infants with a familial risk of ASD to identify early predictors of later ASD development, as well as early mechanisms of disease, compensation and protective factors. Typically these studies are designed to follow children at both high- and low-risk (i.e., siblings of children with and without an older sibling affected by ASD, respectively) from the first few months of life to at least age 36 months, when the diagnosis of ASD is considered stable. Initial findings have suggested that early-life MRI indices can predict later ASD diagnosis by age 2 or later.

Example MRI indices include larger total cerebral volume at 12–15 months (Shen et al., 2013), excessive frontal cerebrospinal fluid at 6–9 and 12–15 months (Shen et al., 2013), and higher white matter fractional anisotropy (FA) values at 6 months (Wolff et al., 2012), and increased cortical thickness in the corpus callosum in the first year of life (Wolff et al., 2015). Most recently, Blasi et al. (2015) quantified differences in fMRI activation in response to human voice sounds and non-voice sounds between high- and low-risk ASD groups during natural sleep: 4- to 7-month-old infants at high risk of ASD exhibited reduced sensitivity to human voices, relative to those at low risk of ASD, during natural sleep. This result suggests the presence of early disturbances in perceptual processing of human voices, which are the most basic and crucial acoustic stimuli in the social environment, will impact later social and emotional development. These neuroimaging findings suggest that longitudinal MRI may serve not only to provide clues for potential biomarkers but also to reveal pathologic mechanisms.

### *MRI Predictors of Prognosis*

Another potentially important application of longitudinal MRI is the prediction of prognosis (i.e., to predict later behavioral and functional outcomes). One example would be the ability to predict whether a child diagnosed with ASD at age 24 months will develop more than minimal verbal skills by age 60 months, which in turn is an important predictor of later-life behavioral and social outcomes (Baghdadli et al., 2007; Billstedt, Gillberg, & Gillberg, 2005; Howlin, Goode, Hutton, & Rutter, 2004; Szatmari et al., 2002). At present, the predictive value of behavioral assessment during early toddlerhood (e.g., joint attention, repetitive behavior, and nonverbal IQ at 2 years) for later language outcomes is limited to identifying ASD children with severe impairments (Anderson et al., 2007; Pickles et al., 2014; Wolff et al., 2014). This leaves a gap in the ability to predict subsequent verbal development for less severely affected children with ASD; this gap might be addressable by longitudinal MRI studies of toddlers.

A recent longitudinal examination demonstrated that prediagnosis fMRI activity at ages 12–48 months differentiated language deficits 1 year later in children with ASD (Lombardo et al., 2015). More specifically, ASD children with poor language outcomes exhibited reduced activation in language-sensitive superior temporal regions in response to speech when compared to ASD toddlers with relatively good language outcomes; activation in this ASD group was also found to be reduced when compared to typically developing children and language-delayed non-ASD children. This finding suggests the potential value of MRI assessment during toddlerhood for identifying objective brain-based prognostic markers of language development in ASD. If successfully obtained, such markers would have the potential to inform decisions regarding the deployment of early intervention efforts, as well as to assess brain responses to intervention.

## Pediatric Anxiety Disorders

Anxiety disorders are the most prevalent forms of psychiatric illness in children and adolescents. From a stratified psychiatry point of view, pediatric anxiety disorders are of interest because: (1) they predict risk for later onset of a second psychiatric illness (e.g., depressive disorder); and (2) their origins appear to lie in the fetal and/or perinatal period. Thus, pediatric anxiety disorders are another example of a potentially rich target for longitudinal evaluation in imaging studies.

### *Pediatric anxiety disorders as predictors of later depression*

Pediatric anxiety disorders are believed to contribute to, or at a minimum signal the likelihood of, the development of secondary psychiatric complications later in life (Woodward & Fergusson, 2001). Cross-sectional and longitudinal studies have consistently identified the presence of anxiety disorders in childhood and early adolescence as a strong predictor of adult depressive symptoms (Beesdo, Pine, Lieb, & Wittchen, 2010; Kessler et al., 2001; Pine, Cohen, Gurley, Brook, & Ma, 1998; Silberg, Rutter, Neale, & Eaves, 2001; Silk, Davis, McMakin, Dahl, & Forbes, 2012; Weissman, Fendrich, Warner, & Wickramaratne, 1992; Weissman et al., 2005). While studies looking at pubertal/adolescent populations have found links between subclinical depressive symptoms (e.g., fatigue, poor concentration) and the later development of major depression in adulthood (Hill, Pettit, Lewinsohn, Seeley, & Klein, 2014; Pine, Cohen, Cohen, & Brook, 1999),

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findings from pre-pubertal studies are less clear in such links. In fact, some have found that previously observed relationships between pre-pubertal-onset depression and recurrence of depression in adulthood do not survive after taking into account the presence of anxiety and externalizing disorders (Weissman et al., 1999).

Consistent with proposed commonalities in symptoms, shared structural and functional correlates of both anxiety and depressive disorders have been reported (Bremner, 2004; Bruhl, Delsignore, Komossa, & Weidt, 2014; Etkin & Wager, 2007; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Miller, Hamilton, Sacchet, & Gotlib, 2015; Schmaal et al., 2015). These mostly include limbic structures (e.g., amygdala) involved in emotion and its regulation, as well as anterior cingulate cortex involved in cognitive control (see Ray & Zald, 2012 for a review). For example, anxiety disorders are associated with abnormalities in MRI metrics of amygdala (e.g., gray matter volume, functional connectivity) not only in adults (Basser & Pierpaoli, 1996; Robinson et al., 2014; Roy et al., 2013), but also in young children (i.e., 7–9 and 12 years old) (Milham et al., 2005; Qin et al., 2014). For depressive disorders, nearly all MRI studies that focus on adults also highlight alterations (e.g., gray matter volume, functional connectivity) in the ventral anterior cingulate cortex (Bora, Harrison, Davey, Yucel, & Pantelis, 2012; Botteron, Raichle, Drevets, Heath, & Todd, 2002; Carballedo et al., 2011; Drevets, Savitz, & Trimble, 2008; Hastings, Parsey, Oquendo, Arango, & Mann, 2004; Ho et al., 2014; Price & Drevets, 2012; Yan, Cheung, et al., 2013). This region is tightly coupled to amygdala function (Pezawas et al., 2005; Roy et al., 2009) and commonly shows abnormalities in studies of anxiety as well (Bruhl et al., 2014; Drevets et al., 2008).

From the viewpoint of longitudinal study design, individuals affected by pediatric anxiety disorders represent a valuable target for imaging studies aiming to identify biomarkers to predict adult depressive disorders. Additionally, when combined with intervention trials (e.g., cognitive behavioral therapy, serotonin selective inhibitors), longitudinal studies have the ability to address questions regarding the impact of interventions on the neural and behavioral trajectories of those at risk for later development of depression.

To date, there are no published longitudinal MRI studies mapping neural trajectories of individuals diagnosed with pediatric anxiety disorders, in an effort to study later life depression. However, using an alternative approach to studying the development of depression, recent work comparing neural development in children of depressed parents (high-risk) with those of non-depressed parents (low-risk), has provided initial insights. The high-risk group in this work is at increased risk of developing anxiety and depressive disorders relative to the low-risk group (Foland-Ross, Hardin, & Gotlib, 2013; Tau & Peterson, 2010; Weissman et al., 2005). For example, a cross-sectional study conducted by Foland-Ross, Gilbert, et al. (2015) demonstrated that diagnosis-free girls (9–17 years old) in a high-risk group (born to mothers with recurrent depression) had cortical thinning in the anterior cingulate cortex, which was in turn associated with greater difficulty managing sadness. In a longitudinal extension (Foland-Ross, Sacchet, et al., 2015), alterations in cortical thickness, particularly cortical thinning in the orbitofrontal cortex, at ages 10–15 reliably predicted the subsequent onset of depression (i.e., 5 years later). This pioneering work illustrates that longitudinal MRI research can play a role in identifying biomarkers that can better predict individuals at high risk for developing depression.

### *Focus on fetal origins*

A growing literature is documenting associations between early neurodevelopmental stressors and the eventual development of psychiatric illness—particularly pediatric anxiety disorders (Dawson, Ashman, & Carver, 2000; Glover, 2014). Accumulating evidence from animal and human studies shows that prenatal maternal psychological stress (e.g., anxiety, depression) is a risk factor for anxiety disorders in offspring (Buss, Entringer, Swanson, & Wadhwa, 2012; Glover, 2014; Hay, Pawlby, Waters, Perra, & Sharp, 2010; Kingston, Tough, & Whitfield, 2012; Monk, Spicer, & Champagne, 2012; O'Connor, Monk, & Fitelson, 2014; Van den Bergh & Marcoen, 2004). For example, prospective longitudinal studies show that levels of self-reported maternal stress and anxiety during pregnancy predict atypical behavioral/emotional development in infants, such as greater cry responses to novelty (Petzoldt et al., 2014; Werner et al., 2007) and cognitive delay (Davis & Sandman, 2010; Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002). In turn, such atypical behavioral/emotional responses during infancy predict the development of anxiety disorders in childhood and adolescent (Perez-Edgar & Fox, 2005).

Retrospective longitudinal examinations have begun linking prenatal maternal stress to MRI-based brain outcomes in childhood. Sandman, Buss, Head, & Davis (2015) demonstrated significant cortical thinning in children (ages: 6–9 years) with a history of prenatal exposure to maternal depressive symptoms. In particular, maternal depression at 25-weeks gestational age was strongly associated with cortical thinning in the prefrontal cortex, which is coupled with childhood externalizing symptoms. In parallel, prospective longitudinal efforts linking prenatal maternal stress to brain and behavioral developments in offspring of stressed mothers during pregnancy are beginning to emerge. Initial work has successfully linked the increased level of prenatal maternal anxiety to lower values of white matter structural metrics (e.g., FA) at birth (Rifkin-Graboi et al., 2013), as well as slower volumetric growth of the hippocampus over the first 6 months (Qiu et al., 2013). Furthermore, Buss, Davis, et al. (2012) report adverse effects of prenatal exposure to maternal stress hormone on amygdala volume and affective behaviors at the age of 7.

The aforementioned retrospective and prospective longitudinal studies point to the potential benefit of prenatal/fetal MRI studies for understanding the impact of fetal programming on the development of later life illness. Related to

prenatal anxiety, researchers are actively working to clarify the effect of prenatal exposure to selective serotonin reuptake inhibitors (SSRIs)—the most commonly prescribed antidepressants for anxiety disorders and depressive disorders. While epidemiologic studies alone remain a source of confusion due to inconsistences in findings (Eriksen, Kesmodel, Pedersen, & Mortensen, 2015; Odsbu et al., 2015; Ornoy & Koren, 2014), future longitudinal imaging studies focused on the prenatal and neonatal periods may be able to help inform this controversy. In particular, they can provide a mechanistic understanding of possible disturbances associated with SSRIs, if present. Arguably, imaging efforts focused on non-human samples have the greatest potential to inform our understanding of causality, given the ability to experimentally manipulate exposures.

A crucial question for any efforts focused on the prenatal period, is whether fetal MRI is reliably applicable to longitudinal examination (Anderson & Thomason, 2013; Limperopoulos & Clouchoux, 2009; Saleem, 2014; Welsh, Nemec, & Thomason, 2011). Fetal MRI requires interactive scanning to account for a moving fetus (Ferrazzi et al., 2014; Seshamani, Cheng, Fogtmann, Thomason, & Studholme, 2014) and the respiratory motion of the mother (Liu, Glenn, & Xu, 2014). Although fetal MRI remains practically challenging and limited in its availability, recent advances are beginning to reveal the structural (Jakab et al., 2015; Kasprian et al., 2011) and functional (Jakab et al., 2014; Schopf, Kasprian, Brugger, & Prayer, 2012; Thomason et al., 2014, 2013, 2015) organization of the brain during this highly dynamic period. Understanding typical fetal brain development is vital for identifying sensitive periods of vulnerability, in which environmental factors (e.g., exposure to maternal stress) impact most on later psychiatric and neurological disorders. Obtaining such knowledge would be valuable when determining the timing of optimal/effective intervention for these disorders.

## Preterm Birth

Complementing the growing associations between pediatric anxiety disorders and fetal stress is the MRI examination of individuals born preterm. Although life-preserving technologies have raised survival rates up to 85% (Smith, Draper, & Field, 2014), the preservation of life does not assure typical, healthy development. Individuals with a history of preterm birth have three to five times increased risk of neurodevelopmental disorders in childhood (Behrman & Butler, 2007; Glass et al., 2015), such as ASD, anxiety disorders, and attention deficit hyperactivity disorder (Johnson & Marlow, 2011; Treyvaud et al., 2013). This elevated risk mostly continues into adolescence and adulthood (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Allin et al., 2008; Barre, Morgan, Doyle, & Anderson, 2011).

Based on clinical vulnerability of this population, an increasing number of MRI studies has retrospectively examined individuals with a history of preterm birth (i.e., toddlers, children, adolescents, and adults), revealing alterations in multiple MRI metrics (Lubsen et al., 2011), even in individuals born late preterm (Degnan et al., 2015). These include gray matter volume (Ment, Kesler, et al., 2009); FA white matter microstructure assessed by DTI (Duerden, Card, Lax, Donner, & Taylor, 2013); intrinsic functional networks assessed by R-fMRI (Constable et al., 2008; Damaraju et al., 2010), and task-based fMRI activity/connectivity (Carmody et al., 2006; Frye et al., 2009; Myers et al., 2010 ). Some of these MRI studies highlight that the reported abnormalities in MRI metrics, particularly white matter microstructure (e.g., FA), are concurrently associated with neurodevelopmental deficits in children and adolescents born preterm. Examples include mental development at the age of 2 (Counsell et al., 2008), IQ at the age of 12 (Constable et al., 2008), language-related skills at the age of 9–16 years (Feldman, Lee, Yeatman, & Yeom, 2012; Mullen et al., 2011) and 16 years, and short-term memory in adulthood (Finke et al., 2015).

Most relevant to the present work, prospective MRI longitudinal studies following preterm infants from soon after birth have begun, providing valuable insights into developmental trajectories of this vulnerable population (see Kwon, Vasung, Ment, & Huppi, 2014; Ment, Hirtz, & Huppi, 2009). The vast majority of studies have reported the presence of structural (Brown et al., 2014; Kersbergen et al., 2014; Young et al., 2015) and functional (Smyser et al., 2011) MRI aberrancies at birth or during infancy, which are associated with subsequent neurodevelopmental outcomes (Rose et al., 2009; Young et al., 2015). Future longitudinal MRI research can target this high-yield "at-risk" clinical population, scanning from birth, and over the course of time, for providing more precise information regarding prediction of risk and prognosis for neurodevelopmental disorders.

## Specific Learning Disabilities (SLDs)

Specific learning disabilities (SLDs) are uniquely positioned among the various DSM-5 disorders, as they can be readily quantified using a broad range of standardized tests. That is, SLDs are reliably defined by impaired performance, relative to norms, in reading, writing, and/or mathematics. Despite the availability of objective assessments, similar to other psychiatric disorders, SLDs are characterized by marked heterogeneity in clinical presentations (McArthur et al., 2013; Ramus et al., 2003), as well as a high degree of comorbid illness (Germano, Gagliano, & Curatolo, 2010; Willcutt et al., 2010, 2013). Among SLDs, reading disability (i.e., dyslexia) has received the most attention in the MRI literature, with a range of studies examining the neural bases of risk (Raschle, Chang, & Gaab, 2011; Raschle, Stering, Meissner, & Gaab, 2014; Saygin et al., 2013), current impairments (Eckert et al., 2003; Richlan, Kronbichler, & Wimmer, 2011, 2013), and responses to intervention (e.g., Barquero, Davis, & Cutting, 2014). The detection of neural changes associated with widely accepted phonology-based treatments has gained particular attention; convergent results suggest the normalization of dyslexia-associated

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abnormalities in functional activity within the known left-hemisphere reading network in children and adults (Aylward et al., 2003; Eden et al., 2004; Shaywitz et al., 2004; Simos et al., 2007; Temple et al., 2003). Complementing these findings is work suggesting a compensatory reliance on alternative circuits outside the reading network in remediated dyslexic individuals (Eden et al., 2004; Koyama et al., 2013).

### *Identification of non-responders*

Of particular relevance to the present work are findings that the interventions are not equally effective across individuals: 20–30% of children with (or at risk of) dyslexia do not respond adequately to generally effective interventions (see Brown & Felton, 1999; Torgesen, 2000 for a review; Torgesen et al., 1999; Vellutino et al., 1996). This gap could be addressed through the establishment of neurophenotypes at baseline that are predictive of treatment effectiveness, or demonstration of differential patterns of treatment-related brain changes associated with behavioral outcomes. Examples come from recent cross-sectional work suggesting that treatment responders and non-responders (ages 10–14 years) differ with respect to left inferior parietal lobule activation following a 4-week reading intervention (Odegard, Ring, Smith, Biggan, & Black, 2008).

Similarly, despite the lack of a single experimentally specified intervention, Hoeft et al. (2011) demonstrated that initial MRI-based profiles at age 14 years (i.e., right prefrontal activation during phonological processing and FA of right superior longitudinal fasciculus) predict later reading improvement in children with dyslexia at age 16.5 years. The next necessary step is longitudinal MRI examination to identify biomarkers predictive of treatment response (i.e., who will be responders *vs*. non-responders), which can be used to individualize intervention. For this, it is ideal to implement systematic interventions, ideally different types (e.g., attention-based) beyond phonology-based ones.

Similar to other neurodevelopmental disorders, the age of diagnosis in reading disorders should be reduced. At present, although commonly delayed, the signs and symptoms of dyslexia can be readily diagnosed soon after the official start of schooling (6–7 years old). However, as emphasized by a growing literature, behavioral signs and symptoms are detectable as early as in toddlerhood. Early detection of endophenotypes that are most predictive of dyslexia (e.g., phonological awareness, attention, and motor skills) (Gooch, Hulme, Nash, & Snowling, 2014; Thompson et al., 2015), and determination of optimal interventions based upon this information (e.g., phonological training *vs*. attention training), could rapidly change the trajectory of illness in children affected by dyslexia, before their school performance is negatively impacted.

## CONCLUDING REMARKS

The goal of delineating trajectories for typical and atypical brain development across the first 2 decades of life is increasingly in our grasp. As highlighted in the present work, strategic selection of at-risk populations for examination can help to overcome the various logistical challenges inherent to longitudinal imaging examinations, which can otherwise hinder the pace of progress. Focusing on the potential of stratified psychiatry, we have provided illustrative examples of MRI examinations in autism spectrum disorder, pediatric anxiety disorders, and specific learning disorders. For each, we highlighted the scientific rationale and appropriate time windows for developmentally informed longitudinal designs to be implemented. We anticipate that biomarkers predictive of risk and prognosis derived from longitudinal examinations, as well as those capable of monitoring treatment outcomes, will advance the goals of early intervention and even prevention of psychiatric illness.

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