Multimodal Brain and Behavior Indices of Psychosis Risk

Ruben C. Gur

Introduction

Efforts to develop neurobiological accounts of psychopathology have been hampered, on the one hand by lack of tools for linking neurobiology to behavior and on the other hand by the prevailing view that mental illness is caused by environmental and psychological processes that can be understood without the need to "reduce" the explanatory scheme to biology. A brain-based explanation of psychiatric disorders had to develop the methodology to generate such links against a headwind of resistance to the plausibility or need for such an approach. Psychosis was considered a disorder resulting from causes such as early failure of maternal nurturance, and the emerging field of behavioral neuroscience had limited data from animal models or human brain disorders that were relevant to the complexity of behavioral manifestations of psychosis.

Within clinical neuroscience, progress in understanding neural substrates of behavior was based on the clinical-pathological correlation methodology. The contribution of psychology to this approach was the development of "neuropsychological" tests that could establish abnormalities on behavioral domains related to known syndromes of brain damage, such as cerebrovascular disease, seizure disorders, and dementia. Given the limitations of neurological examinations of the CNS, neuropsychological batteries contributed to the diagnostic process by revealing patterns of deficits that could support differential diagnosis and document effects of progressing or improving neuropathology.

Initial application of these batteries to patients with psychosis revealed deficits of a magnitude comparable to that associated with "neurological" disorders, with

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some specificity of profile implicating fronto-temporal brain systems. This work was greeted early on with much skepticism, but as results replicated they contributed to the momentum of searching for neurobiological accounts of psychosis.

The advent of neuroimaging in the 1980s has generated a virtual revolution in the clinical neurosciences by offering reliable parameters of brain structure and function with rapidly improving spatial and temporal resolution. Neuroimaging technology finally offered powerful tools for establishing neural substrates for behavior, and its early application to psychosis has demonstrated abnormalities that could be related to behavioral manifestations. Here psychologists have contributed by designing and applying "neurobehavioral probes" (Gur, Erwin, & Gur, 1992), tasks that targeted specific brain systems and that can demonstrate the recruitment of such systems for their performance. Such tasks have been applied to normative and to clinical populations, enabling the delineation of regional brain networks required for regulating behavioral domains and their failure in brain disorders. The application of this methodology in the study of psychosis has yielded robust markers of the disorder and supported hypotheses on neurobiological processes responsible for its clinical manifestations. The computerized format of these new tasks allowed their adaptation into tests of individual differences that could serve the same purpose as the traditional neuropsychological tests but with much greater efficiency and demonstrated validity for their linkage to brain systems.

A strong motivating factor in the search for neural basis of psychosis has been the accumulating evidence for its heritability. Early studies have demonstrated that psychosis runs in families, and subsequent studies were able to establish that much of this effect is genetic rather than environmental. However, the search for specific genes remained elusive even after GWAS became available. Notably, this difficulty was observed across medicine. Studies comparing phenotypically based disease classifications (case-control designs) had some spectacular successes but for few diseases, while for most disorders a more fruitful approach was to examine continuous "endophenotypes" (Gottesman & Gould, 2003) or "biomarkers" that can be mechanistically linked to gene action. Such genomic studies require large sample sizes, and the increased affordability of neuroimaging and computerized neurocognitive measures allowed us to add the brain and its product, behavior, to the genomic revolution that is currently impacting all other organ systems. Multimodal neuroimaging parameters combined with behavioral measures offer powerful tools for elucidating the neurobiology of behavior and establishing indices of vulnerability to neuropsychiatric disorders.

This chapter will present the process of applying neuropsychological and neuroimaging methodology to understanding normal variability and effects of psychopathology as exemplified in our efforts to understand neural substrates for psychosis risk. I will begin by a brief historical sketch of the study of brain and behavior leading to the application of neuropsychology to the study of psychosis, and proceed to illustrate major findings with this methodology in normative samples and schizophrenia. I will then introduce the novel computerized neurocognitive testing methodology that is grounded in neuroimaging and show how it has been used in large-scale studies to document normative and aberrant functioning, yielding heri-

table measures that can serve as endophenotypes or biomarkers for integration with genomic studies. Converging efforts using multimodal parameters of brain structure and function will be illustrated, and I will conclude by offering some reflections on where we are headed in this endeavor.

A Brief Overview of the Origins of Neuropsychology

It is noteworthy that the role of the brain in regulating behavior is a relatively recent discovery in the history of civilization. The ancient Greeks, for example, believed that courage arose from the heart, reason the head, and "base qualities" the stomach (cf. Finger, 1994). It was not until the thirteenth century that Albertus Magnus concluded that behavior was controlled by the brain, except he (and others) thought that the action was in the three ventricles (Finger, 1994, pp. 18–19): the first processed the five senses, passing images to the middle reasoning and thoughtful ventricle, before being remembered in the final ventricle (Spencer, 1997, p. 424). It was not until René Descartes that the idea was articulated that the seat of the "soul" was in brain tissue (Descartes, 1664). However, for Descartes, who was familiar with brain anatomy, it was incomprehensible that the soul be located in two "separate organs," the cerebral hemispheres. He therefore concluded that the pineal gland, one brain structure that does not have two hemispheres, must be the seat of the soul. Phrenology, much maligned and ridiculed already by the nineteenth century, nonetheless is a discipline that further influenced scientific thinking about brain and behavior. Lacking the tools to investigate the brain itself, phrenologists studied the head and attempted to correlate size and shape of different portions with human "faculties" (cf. Rafter, 2008). For example, large foreheads were said to be associated with intellectual abilities. This methodology was not accepted by the mainstream of science or supported by empirical research, and the whole idea of localizing behavioral domains in brain regions became tarnished (cf. Rafter, 2008, p. 61). Unfortunately, perhaps, the dismissal of phrenology has led to a negative attitude regarding any efforts to localize cognitive "faculties" in specific brain regions.

With that background, a French neurosurgeon, Pierre Paul Broca (1824–1880), reasoned that the criticism against phrenologists might relate to their failure to study important human faculties and link them to direct evidence of brain integrity. He argued that, of all human faculties, speech is both unique and of major importance, and should have a localizable brain structure to support it. Proceeding to search for a patient whose speech abilities were compromised, but who was otherwise not demented, he encountered Monsieur Lelong, an elderly gentleman who suffered a sudden onset of speech loss Broca (1861). By the time he was examined by Broca and his staff, Lelong used only seven words: "yes," "no," "one," "two," "three," "Lelon," (mispronouncing Lelong) and "toujour"—the French word for "always." However, Broca was able to demonstrate that the patient understood speech, and applied his limited vocabulary appropriately. Thus, he used "one" for the number

"one," "two" for the number "two," and "three" for any number larger than two; "yes" for affirmation, "no" for negation, and "toujour" for everything else. Having documented this patient's deficits, Broca was able, upon Mr. Lelong's death, to perform an autopsy that revealed a large lesion in the third frontal convolution of the left hemisphere. The publication of his findings in 1861 presaged the field of neuropsychology.

The Clinical-Pathological Correlation Method

Subsequent neuroscientists have followed Broca's paradigm, which became established as the clinical-pathological correlation method. Thus, Wernicke (1874) documented that lesions more posterior to Broca's area were associated with relatively preserved speech output, but diminished capacity to comprehend speech. Other investigators, such as Jackson (1932), reported that lesions in the right hemisphere produced deficits in spatial abilities. Links between brain abnormalities and behavioral aberrations have also been established in emotional behavior. Babinski (1914) reported a series of patients ($N=16$) with significant brain damage who were characterized behaviorally by denial of symptoms ("anosognosie"), and even unusual jollity about having these symptoms ("anosodisaphorie"). Notably, all these patients had major lesions in the right hemisphere. The British neurosurgeon Wilson described a patient who laughed incessantly, to the point of not being able to eat (Wilson, 1924). Wilson had to overcome the danger of dehydration by sitting at the patient's bedside and yawning deliberately, which induced the patient to yawn long enough for the nurse to feed him. This patient's lesion too was in the left hemisphere. Subsequent studies have indicated that right hemispheric lesions were associated with positive symptoms of jocular affect while left hemispheric lesions were associated with release of negative affect (Sackeim et al., 1982). Thus, both cognitive and emotional processing are disrupted in patients with brain lesions, and different behavioral domains are affected depending on the location and nature of brain damage. Importantly, brain lesions can produce both negative symptoms (i.e., behaviors such as fluent speech or memory that patients can no longer perform at normative levels) and positive symptoms (i.e., new behaviors, such as aggressive or depressed mood) that may emerge because of damage to regions that inhibit or regulate such behaviors.

Neuropsychological Testing

Progress in neurological evidence linking behavioral domains to regional brain function was paralleled by progress in psychometric methodology, allowing for reliable measurement of behavioral performance. For example, to measure verbal output fluency, psychologists have developed standardized tests where a subject is

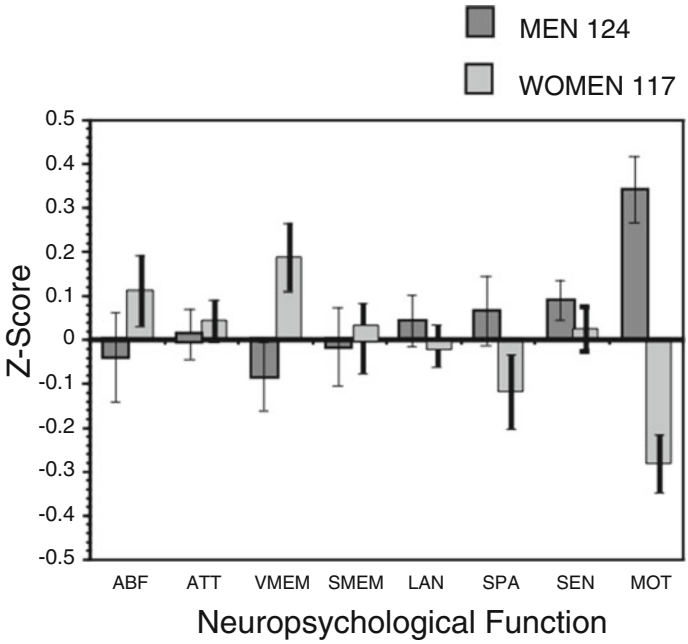

Fig. 1 Neuropsychological profile (±SEM) of healthy men and women, age range 18–45 years, tested with a traditional neuropsychological battery that yields measures of abstraction and mental flexibility (ABF), attention (ATT), verbal memory (VMEM), spatial memory (SMEM), language-mediated reasoning (LAN), spatial processing (SPA), sensory function (SEN), and motor function (MOT). *Z*-Scores are standardized within this sample (adapted from Saykin et al., 1991, 1994)

given a limited amount of time to produce as many words as possible that start with a certain letter (See Benton & Sivan, 2007). Applying such a test in neurological patients proved sensitive to the presence of left fronto-temporal lesions. Similarly, tests of memory proved sensitive to temporal-limbic anomalies, and tests of concept formation and set-shifting sensitive to frontal lobe damage. Research and clinical work using this methodology helped solidify the field of neuropsychology, and it has become the discipline that links behavioral domains to the functioning of brain systems.

Normative studies applying comprehensive neuropsychological test batteries that attempted to measure the main domains of behavior linkable to brain systems have shown sensitivity to normal aging effects and revealed sex differences in several domains (e.g., Saykin et al., 1995). For example, in a study of 241 healthy adults (124 men, 117 women), we have administered a battery that measured abstraction and mental flexibility (ABF), attention (ATT), verbal memory (VMEM), spatial memory (SMEM), language-mediated reasoning (LAN), spatial orientation (SPA), sensory abilities, and motor speed; we found that females outperformed males significantly in verbal memory while males performed better in spatial orientation and motor speed tests (Fig. 1).

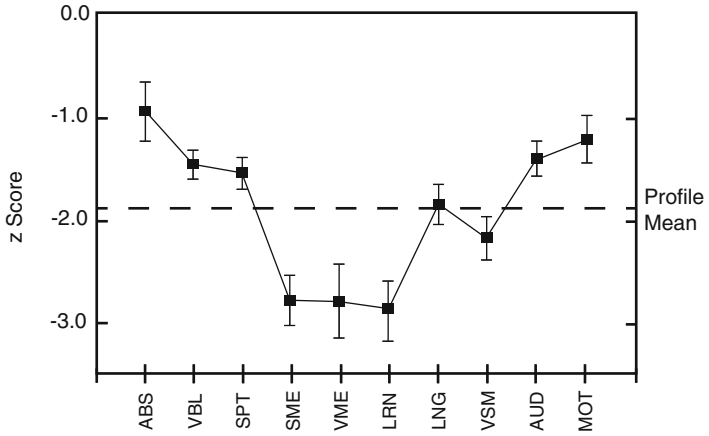

Fig. 2 Neuropsychological profile (±SEM) on a traditional battery for patients with schizophrenia ($n = 36$) relative to healthy controls ($n = 36$) whose performance is set to zero. Functions are abstraction (ABS), verbal cognitive (VBL), spatial organization (SPT), semantic memory (SME), visual memory (VME), verbal learning (LRN), language (LNG), visual-motor processing and attention (VSM), auditory processing and attention (AUD), and motor speed and sequencing (MOT) (from Saykin et al., 1991, Fig. 1)

The finding of sex differences in neuropsychological measures was not novel in itself; sex differences in performance have been described in the literature since the inception of psychometric research. However, the appearance of robust differences on tests that could be linked to specific brain systems begged the question of sex differences in brain structure or function. Such a possibility was considered almost untenable in view of the rising call for sex equality. There was a justified fear that any findings on brain differences between the sexes will reinforce the regressive view that women should stay out of certain professions. Of course, such claims would be resting on the false belief that differences beget inequality and ignore the obvious fact that these differences in average performance, even with large effect sizes, do not apply to all individuals. The differences we observe in neuropsychological measures resemble sex differences in height and weight rather than sexually dimorphic differences such as having a penis or a vagina. Men on average are taller and heavier, yet we can readily think of women who are taller and heavier than most men or men who are shorter and lighter than most women.

In the first study applying a neuropsychological battery in a sample of individuals with schizophrenia compared to demographically balanced healthy controls, we found that patients were impaired across domains, with moderate to large effect sizes, but there was clear differential impairment in all episodic memory tests (Saykin et al., 1991, Fig. 2). This finding suggested the primacy of mesial temporal structures in the cognitive impairment associated with schizophrenia. Subsequent studies showed that the impairment can be seen already in first-episode, drug naïve patients (Saykin et al., 1994), which motivated studies to examine individuals in the

prodromal phase of the disorder and even younger individuals at risk for psychosis. These results were replicated by multiple studies, as indicated in meta-analyses (e.g., Heinrichs & Zakzanis, 1998).

Neuroimaging Effects on Neuropsychology

Progress in neuropsychology has accelerated exponentially with the advent of neuroimaging. In the late 1970s and early 1980s, several methods became available for safely and reliably measuring brain function and structure in humans. Among the first methods was the Xenon-133 clearance technique, which demonstrated that cerebral blood flow (CBF) increases during cognitive activity compared to a resting ("default mode") state, and that it increases more to the left hemisphere for a verbal-reasoning task and to the right hemisphere for a spatial task (Gur & Reivich, 1980). In the first study comparing males and females in CBF, we found in a sample of 62 young and healthy individuals that females had consistently higher values than males across conditions, including the resting ("default mode") state, and greater right hemispheric activation than males for the spatial task, suggesting more effort (Gur et al., 1982, Fig. 3).

This methodology was augmented by positron emission tomography (PET), which allowed measurement of both CBF and metabolism with three-dimensional resolution. Spatial resolution was low (~1.5 cm) at the beginning but reaches 3–4 mm^3 with modern devices. The introduction of magnetic resonance imaging (MRI) has vastly enhanced the scope and pace of research linking brain systems to behavior. Because it is non-invasive and does not expose research participants to ionizing radiation, MRI studies can be done in babies and children, which is not possible with the isotopic methods. Furthermore, advanced MRI methodology can generate multimodal information on the brain, with exquisite spatial resolution. MRI affords reliable volumetric data that can be segmented into brain compartments (gray matter, white matter, cerebrospinal fluid), and MRI sequences are available that provide information on white matter connectivity through diffusion tensor imaging (DTI), regional cerebral perfusion with arterial spin-labeling methods, and resting state connectivity and response to neurobehavioral probes with blood oxygenation level-dependent (BOLD) measures. Application of these methodologies has generated more precise models of brain system involvement in regulating behavior. For example, functional MRI (fMRI) studies have shown lateralized activation in homotopic regions for verbal and spatial complex cognitive tasks (Gur et al., 2000), with sex differences indicating more focal activation for males during the spatial task and for females in response to the verbal task, and activation of the frontal system when participants were deliberating ethical dilemmas (e.g., Avram et al., 2014; Schneider et al., 2013; Shenhav & Greene, 2014; Yoder & Decety, 2014).

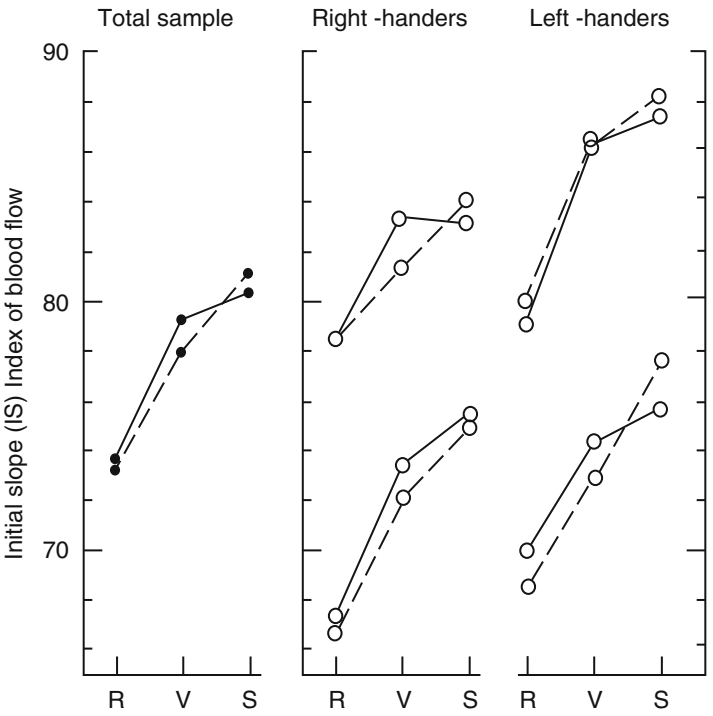

Fig. 3 Initial slope (lS) index of cerebral gray matter blood flow to the left *(solid lines*) and right (*dashed line*) hemispheres for the total sample (*left panel*) and for right- and left-handed females (*circles*) and right- and left-handed males (*squares*) during resting baseline (R) and performance of verbal (V), and spatial tasks (S) (from Gur et al. 1982, Fig. 1)

Application of fMRI tasks in patients with psychosis has helped elucidate neurocognitive abnormalities and identify brain regions that show failure of recruitment associated with poor performance. For example, using the oddball paradigm where participants are requested to respond to an infrequent target with equally infrequent novel distracters, we found that patients with schizophrenia under-activated attentional network for targets and over-activated receptive regions for novel stimuli. These effects correlated with their failure to respond to targets and with neurocognitive measures of attention performance (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; see also Ford et al., 2004).

While the focus of traditional neuropsychological measures was on "cold cognition," activation studies have examined recruitment of brain regions in response to emotional stimuli, and these studies have reveled a cortico-limbic system that is engaged in emotion processing. Early studies have shown consistent sex differences, with females outperforming males across social cognition task. Correspondingly, females also show more focal and less extensive activation for a task requiring discrimination of facially expressed emotions (Fig. 4).

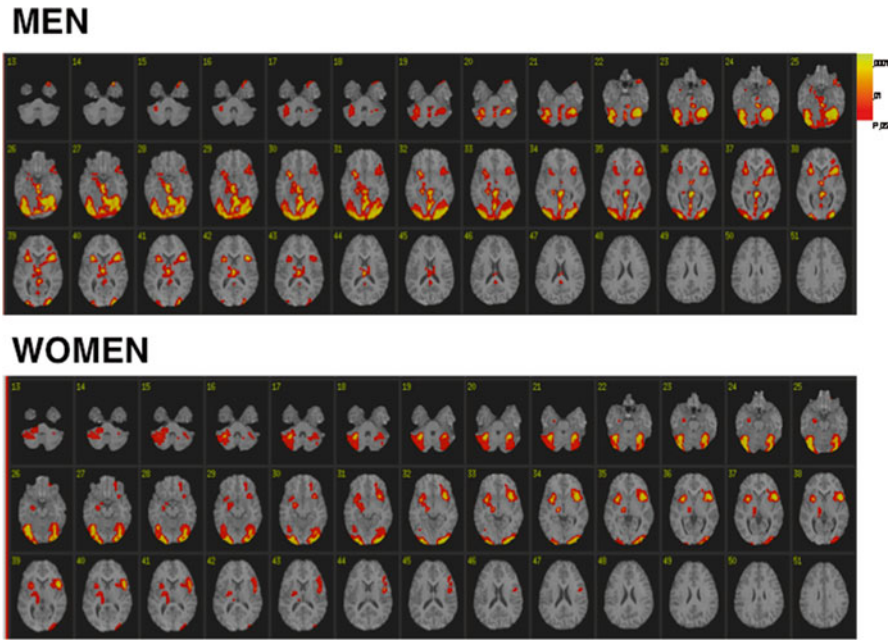

Fig. 4 Activation maps for the contrast of the emotion identification task with baseline in males (*top panel*) and females (*bottom panel*) (based on data from Gur et al., 2002)

Early studies of social cognition in psychosis have indicated deficits in performance of facial emotion processing (Heimberg, Gur, Erwin, Shtasel, & Gur, 1992; Hooker & Park, 2002; Kee, Kern, & Green, 1998). Applications of emotion processing tasks in psychosis have indicated both abnormal activation in limbic regions and failure to activate these regions. Applying a hybrid design to a sample of 16 patients and 17 healthy demographically balanced controls, we found that patients failed to activate limbic (amygdala, hippocampus) and inferior frontal regions, as well as thalamus for the task of identifying emotions. However, an event-related analysis showed that patients over-activated the amygdala in response to fearful faces (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; see Fig. 5), and this over-activation was associated both with errors of identification and severity of negative symptoms.

Such studies have also demonstrated the developmental trajectories of different brain systems and showed, for example, that frontal lobe regions related to executive function do not mature until early in the third decade of life (Giedd et al., 1996; Giedd & Rapoport, 2010; Jernigan et al., 1991; Matsuzawa et al., 2001). In addition to their theoretical value in informing us about typical maturational processes as reflected in brain parameters, these findings have relevance to criminal culpability of adolescents and of individuals with frontal lobe damage (Gur, 2005; Gur & Gur, 2015).

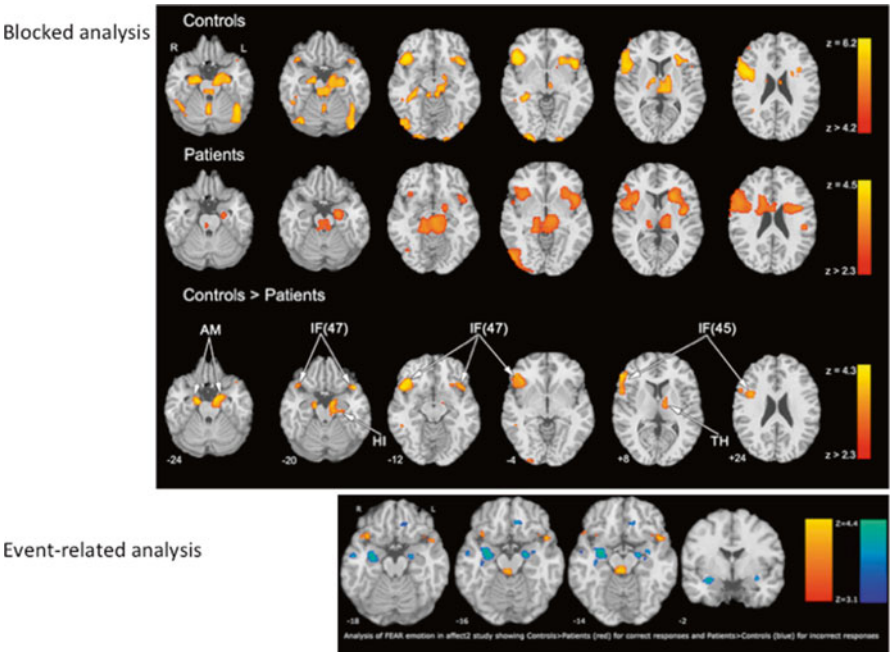

Fig. 5 Regions activated for emotion identification task relative to baseline (block analysis) in controls (*upper row*), patients (*middle row*), and the controls–patients contrast (*bottom row*). No patients–controls contrast survived correction. Images are displayed over a Talairach-normalized template in radiological convention (left hemisphere to viewer's right). The *z*-level coordinates are provided. *AM* amygdala; *IF* inferior frontal (Brodmann area 47); *HI* hippocampus; *IF* (45) inferior frontal (Brodmann area 45); and *TH* thalamus. Event-related analysis, however, showed that patients overactivated the amygdala in response to fearful faces (bottom insert). Based on Gur et al. (2007). *Archives of General Psychiatry, 64*(12), 1356–1366

The Development of Computerized Neurocognitive Testing

With the accelerated application of neurobehavioral probes in functional neuroimaging studies, it became evident that the standard neuropsychological battery is no longer adequate for representing our ability to measure behavioral parameters linkable to brain systems. Many tasks applied in functional neuroimaging studies were not suitable for using as measures of individual differences in performance for several reasons, but some needed minor adjustments emanating for the difference in goals between task administration during scanning and during measures of individual differences outside the scanner. Perhaps most importantly, normative functional neuroimaging studies try to minimize individual differences in performance, since they would confound interpretation of task effects. Since the effort is on identifying a network of regions necessary for performing a task, it needs to be as easy as possible, hopefully generating no errors since they would mean incomplete data for analysis and frustration or anxiety in participants, potentially activating

extraneous brain systems. By contrast, tests designed to measure individual differences need to be difficult enough to separate good from poor performers, and have established psychometric properties of reliability and validity. We have developed such a battery and validated it against traditional measures (Gur, Ragland, Moberg, Bilker, et al., 2001), fMRI activation patterns (Roalf et al., 2014) and as sensitive to sex differences and age effects (Gur et al., 2010). The battery showed deficits in patients with schizophrenia (Gur, Ragland, Moberg, Turner, et al., 2001), associated with flat affect (Gur et al., 2006).

The computerized format of the battery enabled its application in large-scale clinical and genomic studies (Almasy et al., 2008; Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; Roalf et al., 2013; Yokley et al., 2012), demonstrating moderate heritability as well as deficits in patients with schizophrenia and relatives. We have made it freely available for qualified investigators (i.e., working with an Ethics Board oversight) on the web, and multiple laboratories are using it across the globe. It thus offered potential biomarkers for genomic studies that can be linked to brain parameters, and is being used for this purpose by projects such as the Human Connectome (Van Essen & Barch, 2015) and the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA). The computerized format also allowed us to abbreviate the battery and generate multiple forms, which are needed for large-scale longitudinal studies. We were therefore poised to apply it in the Philadelphia Neurodevelopmental Cohort (PNC).

Findings from the PNC

Raquel Gur described the PNC in her chapter, and here I will illustrate how the computerized neurocognitive battery helped capitalize on the wealth of data on brain parameters and behavior available on this sample. Examining the neurocognitive measures alone, we found that they were highly sensitive to age effects, showing steady and significant annual improvement across the age range (Gur et al., 2012), permitting the reliable creation of "growth charts" for neurocognitive development (Gur et al., 2014). Notably, participants who were rated at clinical risk for psychosis showed neurodevelopmental delay greater than that seen in participants at risk for other psychiatric disorders (Fig. 6). This delay is observed already at age 8, several years before the typical age of onset of psychosis. This finding raises the possibility of early detection by combined clinical and neurocognitive data.

The battery also showed robust sex differences across the age range, not only replicating findings from earlier studies with traditional batteries but also highlighting the general complementarity of the sexes. Only 4 of the 26 measures (12 accuracy and 14 speed) showed absence of sex differences (Fig. 7). This finding supports the hypothesis that sex differences in behavior improve the adaptability of our species by enhanced complementarity. It is also important to point out that effect sizes for these differences are small to moderate and the overlap far exceeds one that would justify extrapolation to single individuals.

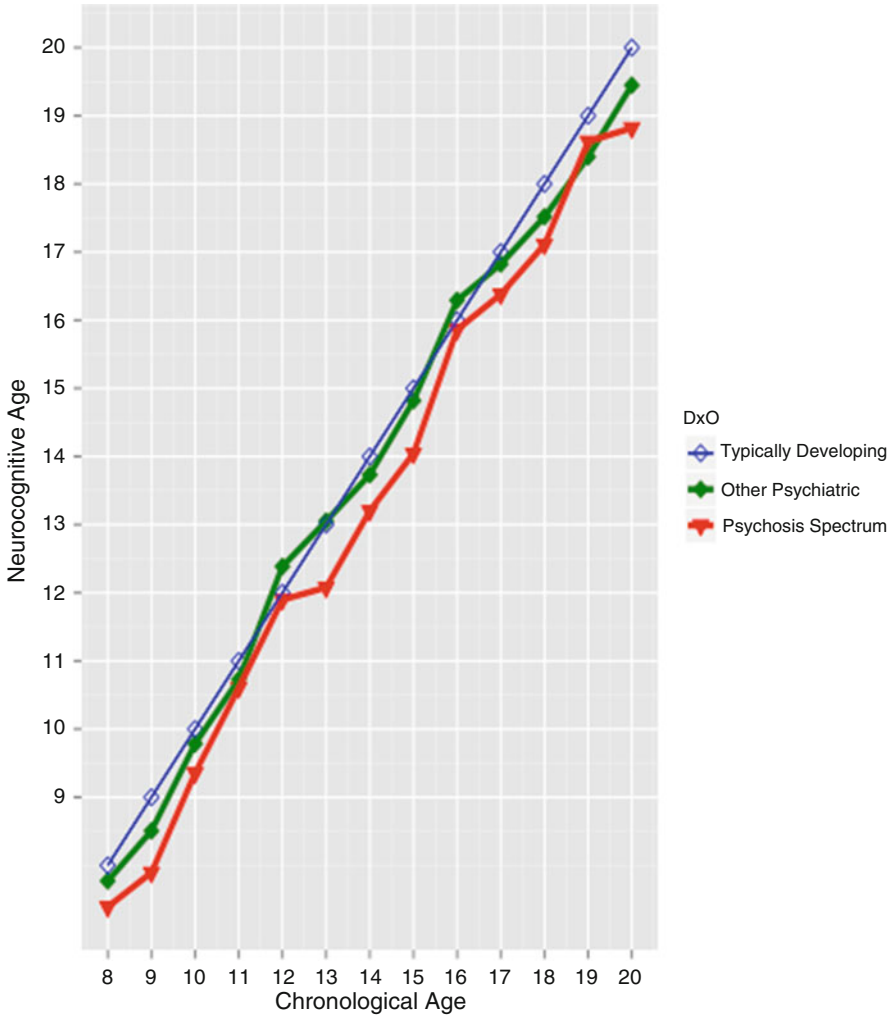

Fig. 6 Chronological age compared with predicted neurocognitive age in years for typically developing, psychosis spectrum, and other psychiatric groups from the PNC sample. Growth charts are provided for predicted age based on averaging all neurocognitive scores (all domains) (partly based on data from Calkins et al. 2014)

Examining performance across the age range of 8–21 years, we found that both accuracy and speed improve in every subsequent annual age cohort. However, the age-related increase in performance had different rates in males and females, reflecting sex differences in brain maturation (Roalf et al., 2014, Fig. 8). Note that we do not imply trajectories in this cross-sectional study; longitudinal designs are necessary for such terminology. However, notwithstanding the limitations of a

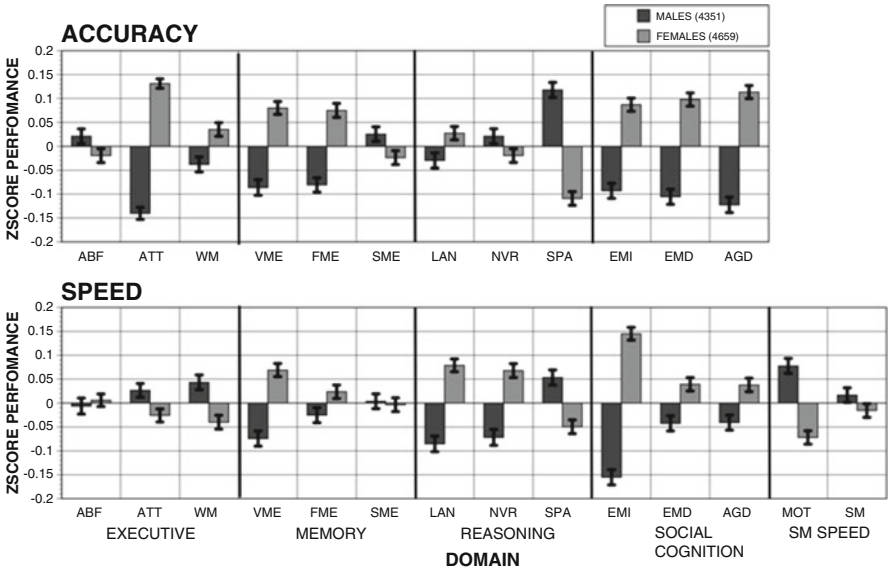

Fig. 7 Neuropsychological profile (±SEM) of males and females from the PNC sample, age range 8–21 years, tested with a computerized neurocognitive battery that yields measures of executive functions: abstraction and mental flexibility (ABF), attention (ATT), working memory; Episodic memory: Verbal (VME), facial (FME), spatial (SME); Reasoning: Language (LAN), nonverbal-matrix (NVR), spatial (SPA); Social cognition: Emotion identification (EID), emotion intensity differentiation (EMD), age differentiation (AFD); as well as motor speed (MOT) and sensorimotor coordination (SM). *Z*-Scores are standardized within this sample and are shown for the 12 accuracy (*top panel*) and 14 speed (*bottom panel*) measures (from Roalf et al., 2014, Fig. 1)

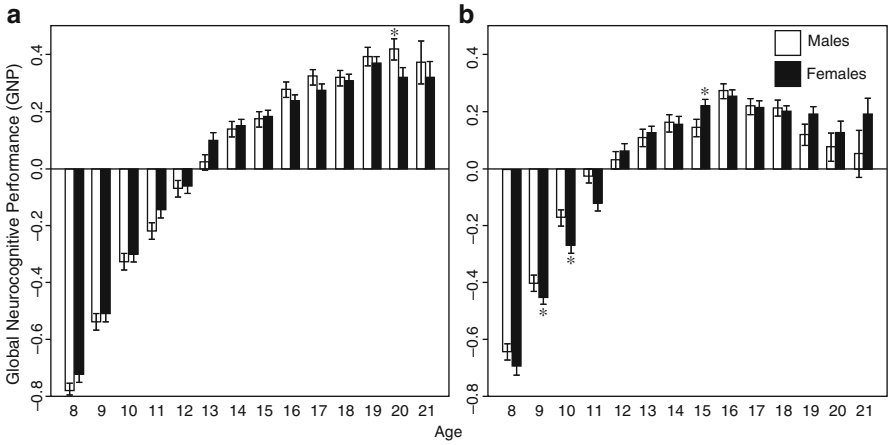

Fig. 8 Means (±SEM) global neurocognitive score (GNP) for accuracy (A) and speed (B) in females (*dark bars*) and males (*light bars*) across the entire sample ($n = 9010$). As expected, GNP accuracy and speed improved with age. Overall, females had higher GNP for accuracy and speed scores than males. Females reach mature performance earlier; however, young adult males outperform females in accuracy but not speed. *Asterisks* (*) denote age-specific sex differences (from Roalf et al., 2014, Fig. 2)

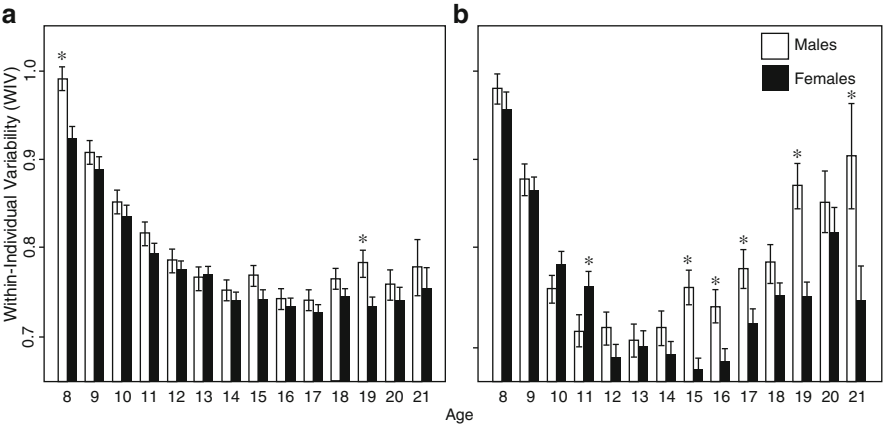

Fig. 9 Means (±SEM) for across-test within-individual variability (WIV) for accuracy (A) and speed (B) in females (*dark bars*) and males (*blue bars*) across the entire sample (n = 9010). As expected, males have higher accuracy and speed WIV as compared with females. In general, accuracy WIV decreases with age and younger males (age 8) show the highest variability, but then variability increases with age, especially for speed, after around age 17. Higher values represent higher variability. *Asterisks* (*) denote age-specific sex differences (from Roalf et al., 2014, Fig. 3)

cross-sectional design, the results show striking age cohort effects and putative rates can be discerned.

The computerized measures also permitted calculation of within-individual variability (WIV), an index reflecting the degree of "cognitive specialization." Expectedly, maturation occurs in stages and hence WIV decreased with higher age from childhood through adolescence as neurodevelopmental lags are overcome. Unexpectedly, we found that WIV increases after about age 17 and on to young adulthood, an effect especially pronounced for speed (Fig. 9).

We interpreted this effect as reflecting the emergence of cognitive specializations related to skill-honing and brain maturation. The sex differences in WIV are consistent across all age groups, with males having higher values, indicating that males tend to be "specialists" and females "generalists." This finding is consistent with a hypothesis dating back to Darwin's (1871) observation that evolution is associated with greater within-species variability, and the dawn of psychometrics was marred by studies showing higher variance in male performance (not WIV, but sample variance) being used to justify discrimination against females in higher education (Thorndike, 1906, but see Hollingworth's eloquent response). The finding of higher WIV in males further supports complementarity between the sexes, as both "specialists" and "generalists" are needed for prosperous survival. That these differences should not be used as a basis for sex discrimination is obvious since there was no overall sex difference in performance in this sample (Roalf et al., 2014).

The multimodal neuroimaging data yielded rich novel information on brain development related to neurocognition. Replicating earlier work (e.g., Giedd et al., 1996; Jernigan et al., 1991; Matsuzawa et al., 2001), gray matter volume declines

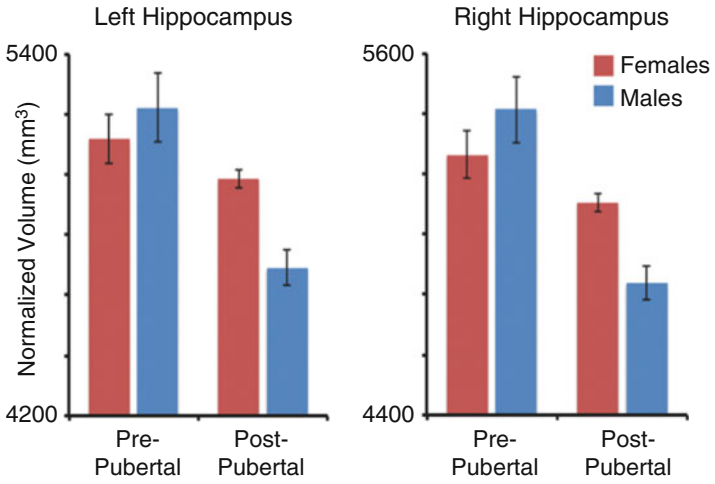

Fig. 10 Sex differences in the impact of puberty on hippocampal volume (mean ± SEM). Prepubertal males and females have similar hippocampal volumes. However, postpubertal males have significantly reduced hippocampal volume compared to postpubertal females. Reported volumes control for intracranial volume (ICV), subject age, and an age-by-sex interaction (from Satterthwaite, Vandekar, et al., 2014, Fig. 2)

during this age range while white matter and cerebrospinal fluid volumes increase. However, regional differences are pronounced, and these diverge between males and females in ways that relate to cognitive performance. For example, hippocampal volume shows less age-associated decline in females than males, resulting in higher volumes in adult female that related to their better performance on episodic memory tasks (Satterthwaite, Vandekar, et al., 2014 Fig. 10).

CBF was also measured in the PNC study, and it showed marked sex differences consistent with our findings with the isotopic studies described above. Since isotopic methods are not permissible in children, our data on the age range of 8–18 were entirely novel. They indicated that CBF declines with increased age group in both males and females until the age of 14–15, where sexes diverge with increasing values in females and decreasing values in males. By age groups older than 18 we observe the higher values in females that were reported with isotopic methods (Satterthwaite, Shinohara, et al., 2014 PNAS, Fig. 11).

With respect to identifying brain parameters associated with psychosis risk, the findings from the PNC support the hypothesis that individuals at risk have similar abnormalities to those seen in patients with schizophrenia. For example, the high-risk group showed failure to recruit frontal systems involved in working memory while performing a working memory task in the scanner. The same group *over-activated* the amygdala for fear stimuli while performing a facial emotion identification task (Wolf et al., 2015 , see chapter by RE Gur in this volume). This effect parallels the finding in patients with schizophrenia described above. Such findings

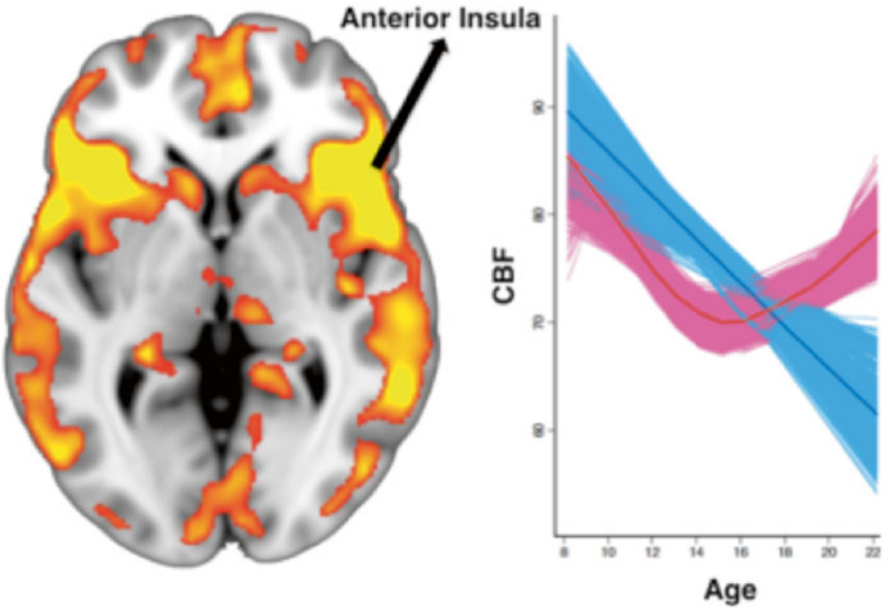

Fig. 11 A voxelwise general additive model (GAM) revealed that the developmental pattern of CBF age-related effects differed significantly between males (*blue*) and females (*pink*) in multiple regions within heteromodal association cortex. Whereas CBF values decline in males and females until late adolescence, CBF in females increased thereafter. Images thresholded at $Z > 4.9$ (Bonferroni $p < 0.05$), $k > 100$; age plots depict GAM fit for each voxel in the inferior insula cluster, stratified by sex and adjusted for model covariates (from Satterthwaite, Shinohara, et al., 2014 [PNAS], Fig. 2)

buttress the hope that a dimensional approach, as envisioned by the RDoC initiative (see several chapters in this volume), can lead the way to biologically based mechanistic accounts of psychopathology.

The multimodal neuroimaging of the PNC sample also included DTI and resting-state connectivity. These parameters also yielded robust sex differences, further supporting the complementarity hypothesis. Analysis of structural connectivity based on the DTI showed that in males the predominant connections were within-hemispheric, while in females inter-hemispheric connections predominated (Ingalhalikar et al., 2014). Examining functional connectivity with resting-state BOLD, Satterthwaite, Vandekar, et al. (2015) found robust sex differences, with males displaying more between-module connectivity while females demonstrated more within-module connectivity. Furthermore, the degree to which a given participant's cognitive profile was "male" or "female" was significantly related to the masculinity or femininity of their pattern of brain connectivity. We have also observed deficits in connectivity associated with psychosis risk (Satterthwaite, Wolf, et al., 2015; see RE Gur's chapter in this volume).

Summary and Future Directions

In this chapter, we have attempted to summarize the background for current efforts to construct a theory of psychopathology based on links between brain systems and neurocognitive domains, "cold" and "hot". The road is only beginning, current studies examine single modalities, or at most two modalities at a time, and more advanced methodology is needed to integrate the multitude of parameters generated by increasingly sophisticated neuroimaging technology. The complex mission of selecting which brain and behavior parameters are most suitable for use as biomarkers in genomic studies is still nascent, and robust methods for reducing the high dimensionality of these data are still being investigated. Our group is pursuing this effort, but we have shared the data with the larger scientific community on dbGaP and are delighted to see that many groups are working on this dataset and reporting novel findings.

Notwithstanding the daunting task ahead, hopefully this chapter also conveys a sense of progress. We have traversed quite a distance from relying on lengthy paper-and-pencil batteries administered to scarce groups of patients with brain damage to having data on thousands of individuals with multiple clinical, neurocognitive, and brain structural and functional parameters. We are facing an embarrassment of riches, and hopefully the exposure of the wider scientific community to these data will enhance the rate of knowledge and improve our ability to detect aberrations and intervene early, before the proverbial train has already derailed. Behavioral neuroscience is poised to take a major role in adding the brain to the other organs that can benefit from the transition to "precision medicine".

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