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Personal reflections on observational and experimental research approaches to childhood psychopathology

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Abstract

The past 50 years have seen dramatic changes in childhood psychopathology research. The goal of this overview is to contrast observational and experimental research approaches; both have grown more complex such that the boundary between these approaches may be blurred. Both are essential. Landmark observational studies with long-term follow-up (Robins, 1966; Yarrow, Campbell, & Burton, 1970) have had – and continue to have – unique impact on clinical research and practice. Epidemiological studies showed high rates of psychological disorder and their close tie to neurological impairment (Rutter, Tizard, & Whitmore, 1970). These studies have current impact with respect to brain imaging correlates of clinical outcome. Pharmacological studies, particularly those on stimulants and on treatment of pediatric obsessive compulsive disorder (OCD), have propelled experimental methodology and inspired translational approaches. Predicted future trends are: more informed subgrouping of our heterogeneous phenotypes, reliance on multicenter trials, and documentation of non-conventional methods of care delivery.

Keywords

Attention deficit hyperactivity disorder; child psychiatry; childhood onset schizophrenia; epidemiology; experimental research; follow-up studies; observational research; obsessive compulsive disorder; pervasive developmental disorder; stimulants

It is an honor to be part of the 50th Anniversary tribute to this *Journal* which has, and still does, play an integral part in my postgraduate education. The invitation to contrast the role of observational and experimental research is a tribute to the growing importance of evidence base in our field. The boundaries between ‘observational’ and ‘experimental’ are fuzzy; but I will take observational studies to refer primarily to epidemiological work, and to a lesser extent clinical observation and insights. The term ‘experimental’ covers somewhat narrower ground centered for the child psychiatrist on controlled clinical trials and comparisons between children with a mental illness and their typically developing counterparts on a host of neurobiological markers relating genes, brain and behavior. Although there is perhaps a shift towards experimental studies in child psychiatry, there will be no judgment of these as opposing methods. In the observational realm, epidemiological studies impress in part by their tight focused hypotheses, but many ‘well controlled’ trials are trivial. But more on this later.

As a Swarthmore college undergraduate experimental psychology major, I was influenced by Wolfgang Kohler who, through his work on problem solving in chimpanzees, showed

that complex behavior could be studied as rigorously as the putatively smaller and simpler behavioral units favored by most experimental psychologists, such as human learning lists of nonsense syllables, or rats learning to escape ever more complex mazes (Kohler, 1949). While Gestalt psychology never became a dominant movement in psychology, its legacy – that global behavioral units were amenable to scientific scrutiny – created an ideal ‘set’ for a future research psychiatrist.

Coming from this rigorous empirical background, clinical training in child psychiatry in the 1960s was disappointing: largely psychotherapeutic in nature and indifferent to evidence. The lack of solid scientific grounding was more pronounced in child than adult psychiatry, the latter at least being relatively replete with psychopharmacological studies. However, all was not lost in the Labyrinth of Pediatric Psychopathology: certain key studies provided Ariadne’s threads for the future researcher. In these studies the observational and experimental approaches were intertwined (to draw out the thread metaphor) and form the tapestry of this selective review. Equally important has been the setting for my own research at the intramural program of the National Institute of Mental Health (NIMH), where stable funding, a biomedical setting, and encouragement to take risks enabled intense longitudinal studies of healthy and ill populations, including studies of rare patient groups, utilizing both observational and experimental approaches.

Observational studies

Several landmark observational studies had sufficient impact as to help define generations of future research – the study by Lee Robins described in *Deviant Children Grown Up* (Robins, 1966), the Isle of Wight epidemiological studies of Rutter and colleagues (Rutter et al., 1970), and work by Marian Yarrow (Yarrow et al., 1970) showing the limitation of retrospective data.

Dr. Robins traced 524 individuals who had been St. Louis child guidance clinic patients, locating them in adulthood some 30 years later; the comparison group was 100 normal school children. As 90% were located, the findings were representative. The result, no surprise today, was that the antisocial children had by far the worst outcome in terms of any social, legal, or psychiatric outcome measure. In contrast, the anxiety-disordered patients closely resembled the non-psychiatric controls. This study showed that valid data could be collected in spite of a clinically ‘superficial’ relationship, and it documented that the subjects least likely to be treated psychologically were those most in need of help.

Shortly after the birth of this *Journal*, planning began by Michael Rutter and colleagues for the ambitious and groundbreaking Isle of Wight study. This was a pediatric survey of medical and psychiatric illness and overall functioning in relation to social and cognitive measures. The striking findings of this landmark study from the relatively ‘captive’ island population showed first the overall 6.6% rate of psychiatric disorders in children without physical handicap. The study made clear the lack of appropriate care for these various physical, intellectual, educational and psychiatric disorders (Rutter et al., 1970). Of broadest general interest, however, was the dramatic (39%) rate of psychiatric disorder associated with chronic neurological impairment such as epilepsy or cerebral palsy. Lower IQ or socioeconomic status did not explain the very high rate of psychiatric impairment also found in those with brain disorders. Moreover, while hyperactive inattentive behaviors and psychosis were somewhat more common in the neurologically impaired group, generally the association was not disorder specific. This study inspired a generation of neuropsychological and later, brain imaging studies addressing possible mechanisms by which brain dysfunction mediates psychiatric disorders.

Another follow-up study cast doubt on our professional history taking. Marian Yarrow (Yarrow et al., 1970) documented the weakness of parental retrospective recall of an offspring's toddler years, a building block of clinical child psychiatry. Recollections of early behaviors of 224 toddlers who had attended a research nursery school (where observational notes had been standardized and archived) were compared with these children's personality and functioning at ages 8–9, 13–14, and as adults. A major interpretation of the retrospective data was that current circumstances act as a rather fine screen for recall, drawing recollection of the past in the direction of consistency with the present. Reliance on retrospective data collection was thus called into question (Yarrow, p. 70).

Experimental studies: pediatric psychopharmacology comes of age

Psychopharmacological research is clearly experimental, and the story of stimulant drug treatment is core to the history of child psychiatry. Building on earlier observation of the quieting effects of Benzedrine in restless children having diagnostic pneumoencephalograms (Bradley, 1950), the first truly experimental psychopharmacological studies of childhood were carried out. The early studies of Keith Conners and Leon Eisenberg documented the dramatic effect of stimulant medication on impulsive and inattentive behaviors (Conners, Eisenberg, & Barcai, 1967; Conners & Eisenberg, 1963). Their first study was a small double-blind, placebo-controlled study of methylphenidate (10–30 mg twice daily). The 64 pediatric subjects were a diverse group with predominantly externalizing behaviors, a wide range in cognitive level, and all living in a residential facility. The design was not a cross-over, but a parallel methylphenidate or placebo 10-day trial. The difference in improvement from baseline to day 10 for methylphenidate compared to placebo was highly significant. One lesson to be learned is that when a treatment with a large effect is discovered, methods need not be refined! The immediate and dramatic benefit of stimulants has gratified two subsequent generations of researchers in numerous experimental refinements of Conners' initial observations.

The success of stimulant drug treatment had a dramatic effect on child psychiatry comparable to that seen with antipsychotics in the previous decades in adult psychiatry. At the time, it led to a pseudo-diagnostic use of stimulant drug response because of an unfortunate statement in Bradley's initial report referring to the 'paradoxical' calming effects of Benzedrine. Practitioners began to explain to parents that their children truly had 'brain dysfunction' because they were calmed on stimulants.

This diagnostic practice contradicted my clinical experience in an inner city child psychiatric clinic where families shared bathrooms and medications were therefore not easily stored. On two occasions I had seen healthy siblings of attention deficit hyperactivity disorder (ADHD) clinic patients become even calmer than usual after accidentally taking a stimulant. The idea for a placebo-controlled trial followed, and my own study which documented the similar motor and cognitive responses to stimulant drugs for healthy and hyperactive children (Rapoport, Buchsbaum, & Weingartner, 1980b; Rapoport et al., 1978) would be viewed as an experimental sequel to informal 'clinical' observations.

While clinically the non-paradoxical nature of stimulant drug response has been replicated numerous times (Rapoport & Inoff-Germain, 2002) and the response to the study and its implications gratifying, it nevertheless remains possible that there are diagnostic differences in stimulant effects on brain networks underlying executive function (Vaidya et al., 2005). With newer technology (here, functional magnetic resonance imaging (fMRI) was used), old questions are revived and this study awaits replication.

Our experimental studies related to obsessive-compulsive disorder (OCD) also followed open clinical observations. Early open studies had suggested that clinically, the serotonin

reuptake inhibitor clomipramine (CMI) seemed to be a useful treatment for OCD (Lopez-Ibor, 1968). These open studies had included patients with both depression and OCD, but were crucial in providing both the initial insight as well as data on dosing. A placebo-controlled Swedish study (Bertilsson, Asberg, & Thoren, 1974) provided the first rigorous data documenting the efficacy of CMI for OCD. Our group extended these observations to children (Rapoport, Elkins, & Mikkelsen, 1980a) and, in a second wave of studies, carried out double-blind comparison of CMI with desipramine (DMI), a selective norepinephrine reuptake inhibitor that is an equally effective anti-depressant and antianxiety agent but shows no benefit for OCD (Leonard et al., 1989). This latter approach was better blinded owing to the similar side effects seen with DMI and CMI. A series of patient groups was entered into this CMI/DMI crossover study, including those with severe nail biting (Leonard, Lenane, Swedo, Rettew, & Rapoport, 1991), autism (Gordon, State, Nelson, Hamburger, & Rapoport, 1993), and trichotillomania (Swedo et al., 1989). Perhaps the most creative use of drug treatment effects was the successful trial of selective serotonin reuptake inhibitors in dogs with canine acral lick (Rapoport, Ryland, & Kriete, 1992), a practice which remains standard in veterinary medicine.

These experimental studies were particularly satisfying because the contrast groups and contrast treatments were informative beyond the issue of immediate therapeutic benefit. The groups for whom CMI had a unique benefit showed a behavioral dimension involving repetitive behavior that is not necessarily ego dystonic (as shown in the 1993 autism-CMI study of Gordon et al.). The small but significant benefit for nail biting was also of interest, as nail biting does not appear to be associated with OCD; the necessity of serotonin reuptake inhibition was, of course, intriguing but remains largely unexplained.

Observational studies: childhood onset schizophrenia

While schizophrenia had been observed in children since the first description of the disorder (Kraepelin, 1971), systematic study has been limited. A major observational series by Kolvin and colleagues, however, has had important influence on my own recent work on childhood onset schizophrenia (Rapoport, Addington, Frangou, & Psych, 2005). Kolvin and coworkers documented the existence of a group of children meeting criteria for schizophrenia and representing a later onset population than that found for autistic disorder (Kolvin, 1971; Kolvin, Garside, & Kidd, 1971a; Kolvin, Humphrey, & McNay, 1971b; Kolvin, Ounsted, Humphrey, & McNay, 1971c; Kolvin, Ounsted, Richardson, & Garside, 1971d; Kolvin, Ounsted, & Roth, 1971e). These early observational studies have been amply supported by later work (Nicolson & Rapoport, 1999; Eggers, Bunk, & Krause, 2000; Rapoport et al., 2005) showing phenomenological continuity with the adult disorder, parental characteristics now considered schizophrenia 'spectrum', and the exaggeration of earlier neurodevelopmental impairment seen in more subtle form in adult patients. Similarly, the series of studies by Michael Rutter during this period showed autism and schizophrenia to be distinct disorders with respect to clinical, family, and outcome measures (Rutter, 1968, 1972; Bailey, Phillips, & Rutter, 1996). These combined series of studies structured two new fields of independent research.

As studies of childhood onset schizophrenia expand and mature, however, some old questions reappear. For example, one-third of childhood onset schizophrenia patients met diagnostic criteria for pervasive development disorder (PDD) both before and during the onset of psychosis (Sporn et al., 2004). Second, some forms of language disorder and/or PDD may be risk factors for (or a very early form of) schizophrenia (Clegg, Hollis, Mawhood, & Rutter, 2005). The likely etiologic heterogeneity of both autism and schizophrenia phenotypes complicates the explanation for these findings; it is probable that molecular genetic studies of these disorders will best address this issue (Kilpinen et al.,

2008; Rzhetsky, Wajngurt, Park, & Zheng, 2007; Vorstman et al., 2006) and that some intermediate entities such as multiple complex developmental disorder (Lahuis et al., 2007) will provide a bridge between the two categories.

Speculations for the future

While most reluctant to prophesy the next 50 years, some thoughts about the next decade are offered. These are summarized in Table 1 and discussed in the pages which follow.

Brain imaging: an observational and experimental method

Longitudinal studies have been particularly influential for child psychiatry. In anatomic imaging, an overarching message has been that developmental neuroanatomic trajectories can be more informative than cross-sectional studies or studies conducted at any one age or developmental stage. These developmental trajectories may prove to be useful intermediate phenotypes (Durstun et al., 2005; Addington et al., 2007); cortical trajectories may also reveal a plastic compensatory response to disorder (Rapoport & Gogtay, 2008). The accelerated pattern of cortical 'maturation' in childhood schizophrenia suggests a profound perturbation in a host of developmental processes of myelination and synaptic sculpting. In ADHD the deficits are subtler, but compensatory mechanisms in regions pivotal for the control of attention (Shaw et al., 2006) and delayed cortical development (Shaw et al., 2007a) may explain the convergence to the template of typical development seen in children with ADHD who outgrow the disorder (Shaw et al., 2006, 2007b).

Genetics: observations at a new level

Contributions from genetics have already shown the etiological complexity of most psychiatric disorders. But it is sobering to review the limited effect on clinical diagnosis even for disorders with major Mendelian gene effects (Miller, Begbie, Giacomini, Ahern, & Harvey, 2006). As Miller has outlined, even for syndromes such as Rett syndrome for which a major gene has been found, the clinical syndrome remains important because of the many atypical and spectrum cases with and without the MECP2 gene (Zoghbi, 2003). While there is considerable excitement about copy number variations (CNVs) and autism (e.g., see Weiss et al., 2008), these same rare variations occur for other conditions and often do not track with disease within families (Walsh et al., 2008).

Newer genetic techniques which enable mouse models of the specific genetic alterations seen first in human disorders may ultimately be valuable in understanding childhood psychiatric disorders. For example, in degenerative disorders genetically altered mouse models have enabled proof of concept studies for new biological targets (Albert, 2007). However, clinical breakthroughs have proved illusive and these remain promissory notes (Hardy, in press).

Large-scale multicenter treatment trials

The experimental approach favored today involves large-scale clinical trials. It is hard to evaluate the ultimate contribution of these. The Multimodal Study of Children with Attention Deficit Hyperactivity Disorder (MTA; Richters et al., 1995; Jensen et al., 2001, 2007), and Preschool ADHD Treatment Study (PATS; Kollins et al., 2006; Greenhill et al., 2006) demonstrated the efficacy of psychostimulants in the short term, but the lack of any sustained benefit of this phase of intensive treatment is sobering. The Treatment of Early Onset Schizophrenia Study (TEOSS) has provided useful comparisons across first- and second-generation antipsychotics in early onset schizophrenia (McClellan et al., 2007; Frazier et al., 2007), with the surprising finding of equivalent efficacy for Molindone, a first-generation antipsychotic. Future large-scale clinical treatment trials of particular interest are

those most likely to utilize non-traditional delivery methods and pay greater attention to prevention (Hollon et al., 2002; Clarke et al., 1995).

Because current clinical trials in pediatric psychiatry may not have maximal utility for those actually providing treatment, the Child and Adolescent Psychiatry Trials Network (CAPTN; March et al., 2004) has been created and aims to provide a network of practicing psychiatrists who conduct 'practical clinical trials' involving more 'real life' samples, e.g., those with children having major comorbidities. While this is practically useful, my greatest concern about pediatric psychopharmacology is the lack of conceptually new drugs in the pharmacological industry pipeline.

Long-term prospective cohort studies

We are seeing a rebirth of cohort studies for which there is both dimensional and disorder-based diagnostic data, as well as genetic and environmental assessments. One outstanding example of this approach is the Dunedin New Zealand study which has produced such important data on the early risk factors for, and forms of, adolescent and adult disorders. This study has shown us the power of analysis of genetic risk and environmental stress in outcome for depression and for antisocial behavior (Moffitt, 2005; Caspi & Moffitt, 2006; Poulton et al., 2000; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004). These studies are almost unique in their findings of specific identified genes and specific measured environmental risk factors as they apply to clinical outcomes. An example is the documentation that a functional polymorphism in the gene encoding the neurotransmitter metabolizing enzyme monoamine oxidase A (MAOA) moderates the response to maltreatment in the liability to antisocial disorders (Caspi et al., 2002). While some of these findings await replication, these observational studies have already provided considerable practical benefit, as, for example, documenting the non-trivial nature of selected psychotic symptoms in childhood (Poulton et al., 2000). A limitation of these studies remains the paucity of environmental measures. For example, it is not clear what aspect of early urban exposure is etiologic with respect to ultimate development of schizophrenia. Such studies need to be repeated with refinement of measures and with population subgroups examined more intensely with up-to-date molecular and imaging measures (Caspi & Moffitt, 2006).

Conclusion

Child psychiatry is in a very different place than it was 50 years ago. The pioneering studies cited in this review are now replaced by much more sophisticated, epidemiological, long-term prospective follow-up and multicenter treatment studies. Brain imaging and genetic findings are provocative but, to date, clinical treatment is largely uninfluenced. A wealth of advances in computer science and biotechnology add to the excitement of current research, none of which did we envision 50 years ago.

Key points

- There have been remarkable advances in both observational and experimental research in child and adolescent psychiatry.
- Following classic follow-up approaches, longitudinal prospective data approaches remain very powerful.
- Brain imaging shows great potential; there is already some pay off in delineating disorders (e.g., OCD versus other anxiety disorders), but diagnostic or other clinical uses remain illusive.

- Genetic studies reveal both complexity of early onset disorder and intriguingly nonspecific risk factors such as rare copy number variations.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
CAPTAN	Child and Adolescent Psychiatry Trials Network
CMI	clomipramine
CNVs	copy number variations
DMI	desipramine
fMRI	functional magnetic resonance imaging
MAOA	monoamine oxidase A
MTA	Multimodal Study of Children with Attention Deficit Hyperactivity Disorder
NIMH	National Institute of Mental Health
OCD	obsessive compulsive disorder
PATS	Preschool ADHD Treatment Study
TEOSS	Treatment of Early Onset Schizophrenia Study

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Table 1

Anticipated strengths and drawbacks of research approaches: the next decade

Approach	Research excitement?	Clinical application?	Comment
Epidemiology	Combination of genetics & longitudinal design	Very promising for evaluating risks & gene $\times$ environment interactions	Clearly a growth field
Clinical trials	Newer non-pharmacological techniques & non-conventional delivery of therapy	Practical guidelines from CAPTN; possible more affordable versions of non-pharmacological treatments	Pharmacological industry pipeline weak but other areas promising
Brain imaging	Developmental anatomic brain trajectories of particular interest (e.g., in childhood onset schizophrenia, autism, & ADHD)	Future promise for early diagnosis, understanding recovery	No clinical application yet
Molecular genetics	Exciting, often dimensional, behavioral findings	None yet & none anticipated for major categories	Will have less effect on diagnosis & treatment than anticipated
Animal models	Practical advantages for neurobiological studies	Important in non-biological intervention studies (e.g., for depression)	May be misleading (as ADHD models have been)