Wayne Fenton’s Impact on Academic Neuroscience

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The legacy of Wayne Fenton will undoubtedly include his broad impact upon the academic community of researchers in psychiatry and neuroscience. Although this impact has already been felt, its full breadth and depth can only be anticipated. Eventually, the most profound impact of Wayne Fenton’s legacy will likely be the one Wayne most fervently desired: that people with psychiatric disorders receive better and more effective treatments for their illnesses. By virtue of the MATRICS initiative, this impact will begin in the context of treatments for the cognitive deficits in schizophrenia, which is currently a critical unmet need. Within academic settings, this specific impact is already evident as a resurgence of interest in the neurobiology and pharmacology relevant to cognitive dysfunction in schizophrenia. As envisioned by Wayne Fenton, however, the impact of MATRICS and the other programs he initiated will be broader than “only” the treatment of cognitive deficits in schizophrenia. His vision was to target a drug treatment to an individual symptom domain, individualizing treatment regimens for each patient, without requiring a drug to be effective in all domains. Thus, the particular target of opportunity that provided Wayne Fenton’s focus in the initiation of the MATRICS program is already having an important impact, but in the longer term these efforts will no doubt lead to parallel developments and improvements in the treatment of other psychiatric disorders.

\textbf{Key words:} MATRICS/schizophrenia/cognition

Wayne Fenton began his career as a physician and psychiatrist working at a private long-term care hospital in Washington, doing patient-oriented research.\textsuperscript{4} He saw the functional consequences of chronic mental illness first hand and grappled with the personal devastation that these illnesses brought to patients and their families. Early on he directed his goal toward research as a way to bringing new discoveries to these chronic mental illnesses and understanding to the treating physicians who lack a disease formulation to guide treatment. Even in this private clinical care setting, he worked at discovering explanations through research.\textsuperscript{2,4} Then, in December 1999, Dr. Fenton joined the US National Institute of Mental Health (NIMH) extramural program office, a job that turned into a great opportunity for the field of schizophrenia research: for patients, families, and for the clinical scientists who study the illness. What was so special about Wayne Fenton’s perspective? It was that he had an “working,” clinical understanding of chronic schizophrenic individuals; his extensive clinical expertise gave him an understanding of their needs and the extent of the knowledge gap in their treatment. In addition, he was personally motivated to help them, using his clinical expertise coupled with the power of the NIMH to direct research to the nation’s most pressing clinical needs. He knew the need and paid attention to directing scientific work to the overwhelming clinical burden. He saw that previous approaches had been ineffective in solving problems in treating schizophrenia; so, he adopted new approaches and ideas which he pioneered without reservation or fear of intimidation. His effectiveness at gathering new ideas, recognizing the clinical “winners,” and his constant and tireless attention to “grooming” these approaches made him unusual in his work. His only sense of failure was to miss an important opportunity for clinical progress or to waste time on a doomed plan.

Together with his colleagues at the NIMH, Wayne Fenton identified a critical bottleneck limiting the development of treatments specifically directed at the cognitive deficits in schizophrenia.\textsuperscript{5,6} It had become widely accepted that the domain of cognitive deficits—which has been long recognized as being an important aspect of schizophrenia—is not treated adequately, if at all, by existing antipsychotic treatments. Furthermore, evidence had accumulated that these cognitive deficits are largely responsible for the disappointingly poor functional outcome demonstrated by antipsychotic-treated patients with schizophrenia.\textsuperscript{7} Thus, despite the fact that many antipsychotic treatments have been identified and marketed, the cognitive deficits remain as clinical problems in schizophrenia with most individuals with schizophrenia burdened by significant psychosocial deficits. In

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response, NIMH, under the direction of Wayne Fenton and Ellen Stover, developed an initiative called “Measurement and Treatment Research to Improve Cognition in Schizophrenia” (MATRICS), which proceeded to develop a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated. Wayne’s focus on including Food and Drug Administration (FDA) scientists in this process was a critical element in its success. The NIMH awarded the MATRICS contract to the University of California, Los Angeles (Drs Stephen Marder and Michael Green, coprincipal Investigators), in 2002. With Wayne’s guidance and encouragement, MATRICS gathered the relevant stakeholders in both industry and academia to achieve a consensus and establish an effective path that would enable the FDA to consider registering compounds intended to treat cognitive deficits in schizophrenia, independent of treating psychosis per se.

At the level of basic science, the initial consequence of the MATRICS initiative pioneered by Wayne Fenton has been the marked expansion of interest, discussion, and program development in studies addressing the applications of cognitive neuroscience to potential therapeutic treatments relevant to psychotic disorders. Historically, basic neuroscientists and neuropharmacologists interested in schizophrenia focused primarily on the positive psychotic symptoms of the disorders. The tradition that compounds were only marketed for use in people with schizophrenia if they treated the positive symptoms precluded the development of drugs having therapeutic effects that were limited to improvements in cognitive functions. Instead, attempts to improve the efficacy of treatments for the cognitive deficits focused on combining multiple actions in the same molecule, following on the model of clozapine. That is, more complex drugs having multiple mechanisms of action were sought to first treat the positive symptoms while also having the additional effect of improving cognition. Such an approach forced the field away from specific pharmacological tools that impacted specific molecular targets toward less specific drugs with complex mechanisms and multiple effects and side effects. At a time when our basic science understanding of the substrates of various separable aspects of cognitive function was undergoing a revolution of sophistication and precision, our efforts at intervention in the cognitive functions of patients were becoming progressively less precise and specific. Within the neuroscience community, the most immediate consequence of the MATRICS initiative has been the renewed hope that improvements in our understanding of the neurobiology of cognition have the potential to be translated effectively into improved treatments that could actually be developed and marketed, and thereby become available to treat people with schizophrenia.

The invigoration of cognitive neurosciences occasioned by MATRICS has impacted multiple subspecialties. Drug discovery laboratories around the world have new incentives to pursue the development of compounds having specific pharmacological actions on systems known to modulate cognition in animals. While many of these discovery laboratories are within industry, many academic laboratories also have renewed their interest in exploring pharmacological manipulations of cognitive functions at a very basic level. Given the absence of any established treatments for the cognitive deficits in schizophrenia, preclinical scientists engaged in drug discovery efforts have no certain way to assess the predictive validity of the many cognitive tests available. Hence, current efforts in this area are based primarily on our academic understanding of the theoretical constructs related to cognition, coupled with our understanding of the underlying neurobiology. The meeting organized by the MATRICS Neuropharmacology Committee identified the most intriguing molecular targets, promising compounds, relevant human test measures, and potentially predictive animal models for use in the discovery of treatments that target basic mechanisms related to complex cognitive operations. The potential impact of findings regarding the neurobiology of the several domains of cognition that are affected in schizophrenia has increased as a result of Wayne Fenton’s efforts. Accordingly, basic neuroscientists now have renewed enthusiasm for the refinement of our understanding of the neural substrates of particular cognitive processes. More specific investigations of the influences of neuropharmacological manipulations on these neural substrates are now particularly relevant, as emphasized in the articles derived from the MATRICS Neuropharmacology Meeting that were gathered in a special issue of Psychopharmacology.

Similarly, neuropsychologists have been encouraged to expand upon and refine their approaches to the assessment of the several separable domains of cognition that the MATRICS program identified as being impacted specifically in schizophrenia. For example, an NIMH-funded follow-up to MATRICS systematically assessed the psychometric reliability of specific tests for use in a MATRICS battery of cognitive function that is now publicly available and widely used. Of particular interest in this context for future studies will be the sensitivity with which neuropsychological, cognitive, and functional measures will prove to be responsive to pharmacological treatments. A concerted effort to address this and related issues is evident in the work of another NIMH-funded program fostered by Wayne Fenton and his colleagues: “Treatment Units for Research on Neurocognition in Schizophrenia” (TURNS). This multisite clinical trials network has combined the efforts and academic expertise of several key universities (see http://www.turns.ucla.edu). The clinical trial design developed by the MATRICS program proposes an approach to demonstrate efficacy that will be updated with experience and success. The clinical use of procognitive compounds anticipated by
MATRICS would be as cotreatments in persons with schizophrenia already optimally treated with antipsychotic medications. The “Fenton model” is that the distinct domains of psychopathology in schizophrenia will each have their own distinct treatment, antipsychotics for psychosis and cognition enhancers for cognitive dysfunction, both used together.6

The meaning of the MATRICS initiative to research clinicians, initially, was a validation of the clinical reality that antipsychotic drugs do not treat all serious symptoms in schizophrenia. With the discovery of antipsychotic drugs in the 1950s came the implicit assumption that they would treat psychotic illnesses completely, like insulin treats diabetes. Wayne’s conceptual contribution was to articulate the obvious, that schizophrenia has broader symptom domains than psychosis that need to be targeted with novel pharmacology. Wayne’s practical contribution was his effectiveness at “jump starting” this concept. It was the detail that he introduced into the process that, among other things, was important; one aspect of his approach was to make the consideration of targets, the selections of assessments, and the design of clinical trials methodology, a community project among scientists with parties drawn from government, academia, and industry. This strategy forestalled a fragmented and confused approach to the clinical implementation of the plan. Moreover, the process generated a “blueprint” for proof-of-concept trials in cognition for schizophrenia. As a result, there now exists a common work plan for cognitive treatments that will be widely used for testing cognition treatments in schizophrenia.

Another subspecialty arena that has been reinvigorated by Wayne Fenton’s influence is in the burgeoning area of preclinical predictors and human biomarkers with which to assess potential pharmacotherapeutics in the treatment of cognitive deficits in schizophrenia. The MATRICS Program includes a Biomarkers Subcommittee that is designed to facilitate the inclusion of specific biomarkers in conjunction with clinical tests using the MATRICS Neurocognitive Battery (see http://www.turns.ucla.edu). The supplementation of clinical neurocognitive assessments with biochemical, genetic, psychophysiological, or brain-imaging measures having the potential to serve as biomarkers should facilitate the processes of drug discovery and development. There is a clear need for the identification of predictive pathways from the preclinical rodent models that are essential for the rapid screening of compounds of interest to the first proof-of-concept studies in humans that are essential for go no-go decisions in drug development.9,13 Accordingly, the interest in exploring translational paradigms that are applicable across species and have construct validity for the assessment of cognition has never been higher. Accordingly, the TURNS Biomarker Subcommittee has been complemented by the TURNS Preclinical Subcommittee, which has surveyed experts from academia and industry and assembled a listing of preclinical tests that may have utility as predictive measures of the clinical treatment of cognitive deficits in schizophrenia.14 These preclinical models, as ranked in this survey, are now being used especially by pharmaceutical companies to guide their preclinical drug discovery and validation programs.

The opportunities engendered by MATRICS have also incentivized scientists examining complex cognitive functions in both healthy and ill humans, using powerful modern methods of cognitive assessment, psychophysiology, and brain imaging. Indeed, a series of conferences designed as another follow-up to MATRICS was among the last major projects championed by Wayne Fenton and is currently ongoing. This Program—“Cognitive Neuroscience Measures of Treatment Response of Impaired Cognition in Schizophrenia”—is funded by the NIMH and is designed to bring the modern tools and concepts of cognitive neuroscience to bear upon the assessment of cognitive deficits in schizophrenia and the efficacy of pharmacotherapeutics in ameliorating these deficits (see http://cntrics.ucdavis.edu). This program is generating new integrations and collaborations between previously disparate disciplines of cognitive neuroscience and clinical psychopharmacology. The translation of modern neuroscientific approaches to cognition—in both animal and human models—to be applicable to studies of potential pharmacotherapeutic effects in schizophrenia patients is an exciting new enterprise spawned by the efforts of Wayne Fenton and the MATRICS Program.

The legacy of Wayne Fenton will certainly include his broad impact upon the academic community of researchers in psychiatry and neuroscience. Although this impact has already been felt, its full breadth and depth can only be anticipated. Eventually, the most profound impact of Wayne Fenton’s legacy will likely be the one Wayne most fervently desired: that people with psychiatric disorders receive better and more effective treatments for their illnesses. Wayne had the clinical expertise to identify the most disabling aspects of a dysfunction and to expose it to drug development. By virtue of the MATRICS initiative, this impact will begin in the context of treatments for the cognitive deficits in schizophrenia, which is currently a critical unmet need. Within academic settings, the more specific impact is already evident as a resurgence of interest in the neurobiology and pharmacology relevant to cognitive dysfunction in schizophrenia. This interest is bolstered by the increased recognition of the importance and potential benefits of procognitive cotreatments for schizophrenia. Indeed, several clinical trials are already beginning to test procognitive drugs in schizophrenia, including those of the TURNS initiative as well as other academic and industry projects. As envisioned by Wayne Fenton, however, the impact of MATRICS and the other programs he initiated will be broader than “only” the treatment of cognitive deficits.
in schizophrenia. His vision was to target a drug treatment to an individual symptom domain, individualizing treatment regimens for each patient, without requiring a drug to be effective in all domains. Instead, personalized treatments of a given patient’s specific problems can be envisioned if compounds can be developed, marketed, and prescribed to target specific dimensions of illness. Thus, the particular target of opportunity that provided Wayne Fenton’s focus in the initiation of the MATRICS program is already having an important impact, but in the longer term, these efforts will no doubt lead to parallel developments and improvements in the treatment of other psychiatric disorders.

**Funding**

The National Institute of Mental Health; National Alliance for Research on Schizophrenia and Depression; The Veteran’s Administration VISN 22 Mental Illness Research, Education, and Clinical Center to Dr Geyer.

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