Afterword

William T. Carpenter

The Future of the Schizophrenia Construct and Acquisition of New Knowledge

Professor Ritsner has presented three volumes containing the accumulated knowledge and wisdom developed in the schizophrenia field. Current knowledge is broad and deep, but fundamental challenges remain. Some are as old as Kraepelin’s dementia praecox and Bleuler’s group of schizophrenias. “What is schizophrenia?” is still a critical question. The construct used to develop new insights and guide clinical therapeutics has a profound effect on study designs, research questions,

W.T. Carpenter
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA
and etiological and therapeutic discovery. In this Afterword I will briefly comment on the current paradigm and speculate on a shift that will substantially change the construct and the methods of acquiring knowledge.

Is the Kraepelinian dichotomy dead? The porous boundaries observed between schizophrenia and bipolar disorders, as presently defined, suggest the answer is yes. However, it is important to appreciate how much the definition of schizophrenia has changed since he proposed a disease entity based on the co-morbidity of avolition and dissociative pathology. Bleuler’s postulate that the dissociative pathology was fundamental and primary in all cases, if true, suggested a psychopathological process uniting the various clinical presentations in a single disease concept. However, seemingly without comment, this idea radically changed as Schneider’s symptoms of first rank and Langfeldt’s true versus pseudo schizophrenia became influential. Movement in the direction of emphasis on ego boundary impairment and reality distortion symptoms became almost universal with the criteria-based DSM-III. Its revolutionary diagnostic standardization required only a single first rank symptom to meet criteria A for schizophrenia and excluded consideration of avolitional pathology as a diagnostic criteria. Described in more detail elsewhere [1] this movement minimized attention to cognitive pathology and negative symptoms. The porous boundary with bipolar disorder observed in genetic and environmental risk factors, neuroimaging, cognition, and response to anti-psychotic drugs is not a test of Kraepelin’s concept. Rather, it may represent, at least in part, the heterogeneity of a syndrome based on psychotic features rather than avolition and dissociative pathology. Investigators at the Maryland Psychiatric Research Center have demonstrated substantial differences between schizophrenia patients with the negative symptom pathology compared to schizophrenia patients without primary negative symptoms [2].

It is essential that we recognize the syndrome status of the psychotic disorders including schizophrenia. Doing so immediately raises the challenge of heterogeneity reduction. Does the overlap between syndromes suggest an artificial distinction, or is it indicative of a proportion of patients in each syndrome manifesting similar pathology? For example, depression pathology will be found in almost all bipolar patients, but also in many patients with schizophrenia. A biomarker for depression would be expected to distinguish both groups from non-depressed controls, but may be more robust in bipolar cases. However, including only depressed schizophrenia patients in the schizophrenia cohort could make the difference disappear. This does not suggest that schizophrenia and bipolar are the same disorder. Rather, it suggests that depressive pathology, found in many different diagnostic groups, may be a domain of pathology that merits investigation across diagnostic classes. It would be surprising if, for example, genes associated with vulnerability to depression were not similar in depressed patients from several diagnostic classes. Rather than a genetic marker for a single diagnostic class, this genetic profile could be viewed as marking vulnerability for depression in several discrete disorders and perhaps in the general population as well.

A paradigm shift is essential to maximize progress in the study of schizophrenia. When we recognize schizophrenia as a syndrome, we realize that attempts to define
specific disease entities within the syndrome have not worked with traditional sub-types, but have had some success based on the presence of deficit pathology [2]. Attempts to define dimensions of pathology have been successful. The challenge, then, is to advance the most heuristic approach to deconstructing pathologies associated with syndromes. In the context of the IPSS we put forward a proposal for six pathology domains in 1974 [3] with substantial overlap with the eloquent analysis by Cuesta and Peralta [4] defining eight pathology domains. In the current DSM-V process (I serve as chair of the psychosis workgroup) a series of pathology domains are being considered in addition to diagnostic class. Schizophrenia and other psychotic syndromes would be deconstructed into relevant dimensions representing the pathologies that vary among patients in the diagnostic class and require specific assessment and therapeutic attention. In drug discovery, for example, the paradigm moves away from developing a drug for schizophrenia. Sixty years of producing similar anti-psychotic drugs without discovery for other key domains of pathology illustrates the limited utility of a clinical syndrome. The shift to a deconstruction paradigm defines multiple and separable targets for drug discovery. Therapies for a pathology domain may thereby be effective in multiple diagnostic classes. If this hypothesis is valid, it will transform the developmental pathway for therapeutic discovery. Just as we now have dopamine antagonists with efficacy for psychosis across diagnostic classes, we may come to have a compound or behavioral treatment approved for cognition, avolition, depression, anxiety, and other pathology domains that cross diagnostic boundaries.

DSM-V development is in progress. In addition to the usual diagnostic classes for psychotic disorders, dimensions for anxiety, depression, mania, restricted affect, avolition, cognition, disorganization of thought, delusions, and hallucinations are being field tested. Thus clinical assessments will more closely fit the individual patient’s actual pathology and will position the clinician closer to the issues addressed in personalized clinical care. It may also impact future research designs. Rather than genome-wide association study (GWAS) analyses for genes associated with heterogeneous syndromes, the genetics of specific pathological processes will be addressed. Neuroimaging studies may define the structure, function and chemistry associated with specific pathology domains rather than attempting to define biomarkers for syndromes.

This shift in paradigm is relevant for the future study of pathophysiology. The NIMH is developing research diagnostic criteria (http://www.nimh.nih.gov/research-funding/rdoc.shtml) based on neural circuit concepts of symptom expression. For example, a variety of anxiety and mood disorders may relate to pathology in the fear circuitry involving the amygdala and associated structures. NIMH will encourage investigators to investigate neural circuits related to the symptom or impairment of interest, consider phenotype assessment in animal models and recruit patient subjects from the several diagnostic groups associated with the symptom complex of interest. It is hoped that translational science will be advanced by more clearly assessing genotype/phenotype relationships at the level of brain dysfunction where the neuroanatomy and physiology can be “mapped-on” between human and animal models. This involves explicit recognition of the syndrome status of many
psychiatric disorders where deconstruction into component pathologies is essential, and that patients within each syndrome may vary in the domains of pathology with which they are afflicted.

The impact of this paradigm shift will be substantial. Consider the following examples:

- Instead of searching for genes of heterogeneous syndromes, study designs will seek association of genes with neural circuits, phenotypes and specific domains of pathology.
- Drug discovery will target domains of pathology seeking novel compounds for unmet treatment needs such as cognition and negative symptoms associated with some forms of schizophrenia. Efficacy for a specific domain may be relevant to cases in several diagnostic classes where patients manifest the pathology in question.
- Neuroimaging will focus on anatomy, function and chemistry at the intersection of neural circuit and pathology domain rather than the clinical syndrome level.
- Psychosocial treatments will be directed at pathology that cuts across diagnostic boundaries. Instead of broad-based cognitive remediation for schizophrenia, interventions will be tested with subjects who manifest the target impairment. Thus, tailored CBT will address domains such as depressed affect, avolition, or reality distortion rather than major depressive disorder or schizophrenia.

These three volumes speak to the power and the limitations of the dominant model. A paradigm shift, already reflected in some recent studies, promises a new and more robust approach to understand psychopathology and to more specifically addressing the needs of our patients.

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Contributors to Volume I

**Glen B. Baker**  Neurochemical Research Unit and Bebensee Schizophrenia Research Unit, Department of Psychiatry, University of Alberta, Edmonton, AB, Canada T6G 2G3, glen.baker@ualberta.ca

**Deanna M. Barch**  Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; Department of Psychology, Washington University School of Medicine, St. Louis, MO, USA; Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA, dbarch@artsci.wustl.edu

**Aksel Bertelsen**  Center of Psychiatric Research, Århus University Hospital, Risskov, Denmark, abertelsen@dadmnet.dk

**Stefan Borgwardt**  Department of Psychosis Studies, Institute of Psychiatry, London, UK, sborgwardt@uhsbs.ch

**Chad A. Bousman**  Department of Psychiatry, University of Melbourne, Victoria, Australia, cbousman@unimelb.edu.au

**Stefanie L. Bronson**  Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, USA; Graduate Program in Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA, bronsose@mail.uc.edu

**Lisa Burback**  Neurochemical Research Unit and Bebensee Schizophrenia Research Unit, Department of Psychiatry, University of Alberta, Edmonton, AB, Canada, burback@ualberta.ca

**Bernard J. Crespi**  Department of Biosciences, Simon Fraser University, Burnaby, BC, Canada, crespi@sfu.ca

**Brian Dean**  The Rebecca L. Cooper Research Laboratories, The Mental Health Research Institute, Parkville, VIC, Australia; The Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia, anddali@unimelb.edu.au

**Emmanuel Dias-Neto**  Laboratório de Neurociências (LIM-27), Instituto de Psiquiatria, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP,
Brazil; Laboratory of Medical Genomics and Bioinformatics, Centro Internacional de Pesquisa e Ensino (CIPE) – Hospital AC Camargo, São Paulo, SP, Brazil, emmanuel@usp.br

**Alexandria F. Dilullo**  Neurochemical Research Unit and Bebensee Schizophrenia Research Unit, Department of Psychiatry, University of Alberta, Edmonton, AB, Canada, adilullo@ualberta.ca

**Serdar M. Dursun**  Neurochemical Research Unit and Bebensee Schizophrenia Research Unit, Department of Psychiatry, University of Alberta, Edmonton, AB, Canada; National Science and Technology Institute for Translational Medicine, Ribeirão Preto, SP, Brazil, dursun@ualberta.ca

**Yael Dvir**  Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA, yael.dvir@umassmed.edu

**Yogesh Dwivedi**  Department of Psychiatry, University of Illinois, Chicago, IL, USA, ydwivedi@psych.uic.edu

**Ian P. Everall**  Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia, ieverall@unimelb.edu.au

**Jean A. Frazier**  Child and Adolescent Psychiatry, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA, Jean.Frazier@umassmed.edu

**Cheryl A. Frye**  Department of Psychology, University at Albany-SUNY, Albany, NY, USA; Department of Biology Sciences, University at Albany-SUNY, Albany, NY, USA; The Center for Life Sciences, University at Albany-SUNY, Albany, NY, USA; The Center for Neuroscience Research, University at Albany-SUNY, Albany, NY, USA, cafrye@albany.edu

**Paolo Fusar-Poli**  Department of Psychosis Studies, Institute of Psychiatry, London, UK, p.fusar@libero.it

**Wagner F. Gattaz**  Laboratório de Neurociências (LIM-27), Instituto de Psiquiatria, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil, gattaz@usp.br

**Andrew Gibbons**  The Rebecca L. Cooper Research Laboratories, The Mental Health Research Institute, Parkville, VIC, Australia; The Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia, a.gibbons@mhri.edu.au

**Stephen J. Glatt**  Departments of Psychiatry and Behavioral Sciences and of Neuroscience and Physiology, Medical Genetics Research Center, SUNY Upstate Medical University, Syracuse, NY, USA, glatts@upstate.edu

**Irving I. Gottesman**  Departments of Psychiatry and Psychology, University of Minnesota, Minneapolis, MN, USA, gotte003@umn.edu
Ute Habel  Department of Psychiatry, Psychotherapy and Psychosomatics, Medical School, RWTH Aachen University, Aachen, Germany, uhabel@ukaachen.de

Jaime E.C. Hallak  National Science and Technology Institute for Translational Medicine, Ribeirão Preto, SP, Brazil; Department of Neuroscience and Behavioral Sciences, Ribeirao Preto School of Medicine, University of Sao Paulo (USP), Ribeirao Preto, SP, Brazil, jhallak@fmrp.usp.br

Mark F. Lenzenweger  Department of Psychology, State University of New York at Binghamton, Binghamton, NY, USA; Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA; The Personality Disorders Institute, The New York – Presbyterian Hospital, White Plains, NY, USA, mlenzen@binghamton.edu

Danielle C. Llaneza  Department of Psychology, University at Albany-SUNY, Albany, NY, USA, danielle.llaneza01@albany.edu

Vishal Madaan  Assistant Professor in Psychiatry and Neurobehavorial Sciences, Division of Child and Family Psychiatry, Charlottesville, VA 22908, USA, vishalmadaan@virginia.edu

Daniel Mamah  Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA, mamahd@psychiatry.wustl.edu

Daniel Martins-de-Souza  Max Planck Institute of Psychiatry, Munich, Germany; Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK; Laboratório de Neurociências (LIM-27), Instituto de Psiquiatria, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil, martins@mpipsykl.mpg.de; danms90@gmail.com

Patrick P. McDonald  Molecular Genetics Unit, Department of Biology, University of Western Ontario, London, ON, Canada, pmcdona5@uwo.ca

Philip McGuire  Department of Psychosis Studies, Institute of Psychiatry, London, UK, philip.mcguire@kcl.ac.uk

Gary W. Miller  Center for Neurodegenerative Disease, Emory University School of Medicine, Atlanta, GA 30322, USA; Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA 30322, USA, gwmile@emory.edu

Ghanshyam N. Pandey  Department of Psychiatry, University of Illinois, Chicago, IL, USA, gpandey@psych.uic.edu

Katharina D. Pauly  Department of Psychiatry, Psychotherapy and Psychosomatics, Medical School, RWTH Aachen University, Aachen, Germany, kpauly@ukaachen.de
Luca De Peri  Department of Mental Health, Spedali Civili Hospital, The Psychiatric Clinic, Brescia University School of Medicine, Brescia, Italy, luca_de_peri@libero.it

Anca R. Rădulescu  Department of Mathematics, University of Colorado, Boulder, CO, USA; Department of Biomedical Engineering, Stony Brook University School of Medicine, Stony Brook, NY, USA, Anca.Radulescu@Colorado.EDU

Neil M. Richtand  Cincinnati Veterans Affairs Medical Center, Psychiatry Service (V116A), Cincinnati, OH, USA; Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, USA; Graduate Program in Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA, Neil.Richtand@uc.edu

Michael S. Ritsner  Department of Psychiatry, Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel; Acute Department, Sha’ar Menashe Mental Health Center, Hadera, Israel, ritsner@sm.health.gov.il; ritsnerm@gmail.com

Emilio Sacchetti  Department of Mental Health, Spedali Civili Hospital, The Psychiatric Clinic, Brescia University School of Medicine, Brescia, Italy, sacchett@med.unibs.it

Elizabeth Scarr  The Rebecca L. Cooper Research Laboratories, The Mental Health Research Institute, Parkville, VIC, Australia; The Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia, elscarr@unimelb.edu.au

Shiva M. Singh  Molecular Genetics Unit, Western Science Centre, The University of Western Ontario, London, ON, Canada, ssingh@uwo.ca

Elizabeth A. Thomas  The Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA, bthomas@scripps.edu

Ming T. Tsuang  Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego, CA, USA; Harvard Medical School and Harvard School of Public Health, Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA, mtsuang@ucsd.edu

Cesare Turrina  Department of Mental Health, Spedali Civili Hospital, The Psychiatric Clinic, Brescia University School of Medicine, Brescia, Italy, turrina@med.unibs.it

Antonio Vita  Department of Mental Health, Spedali Civili Hospital, The Psychiatric Clinic, University of Brescia, Brescia, Italy, vita@med.unibs.it

Eberhard O. Voit  Department of Biomedical Engineering, Georgia Institute of Technology, Emory University Medical School, Atlanta, GA 30332, USA; Integrative BioSystems Institute, Georgia Institute of Technology, Atlanta, GA 30332, USA, eberhard.voit@bme.gatech.edu
Daniel R. Wilson  Department of Psychiatry, Creighton University Medical Center, Omaha, NE, USA, wilson@creighton.edu

Lauren Yakutis  Child and Adolescent NeuroDevelopment Initiative, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA, lauren.yakutis@umassmed.edu

Zhen Qi  Department of Biomedical Engineering, Georgia Institute of Technology, Emory University Medical School, Atlanta, GA 30332, USA; Integrative BioSystems Institute, Georgia Institute of Technology, Atlanta, GA 30332, USA; Center for Neurodegenerative Disease, Emory University School of Medicine, Atlanta, GA 30322, USA, zhen.qi@gatech.edu
Contributors to Volume III

Anthony O. Ahmed  Department of Psychiatry and Health Behavior, Georgia Health Sciences University, Augusta, GA, USA, aahmed@georgiahealth.edu

P. Alex Mabe  Department of Psychiatry and Health Behavior, Medical College of Georgia, Augusta, GA, USA, pmabe@mcg.edu

Cali F. Bartholomeusz  Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, VIC, Australia, barc@unimelb.edu.au

Peter F. Buckley  Department of Psychiatry and Health Behavior School of Medicine, Medical College of Georgia, Augusta, GA, USA, pbuckley@mcg.edu

William T. Carpenter  Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA, wcarpent@mprc.umd.edu

Caroline Cellard  Centre de recherche Université Laval Robert-Giffard, Québec City, QC, Canada, caroline.cellard@crlrg.ulaval.ca

Michael T. Compton  Department of Psychiatry and Behavioral Sciences, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA, mcompto@mfa.gwu.edu

Dirk Czesnik  Department of Clinical Neurophysiology, University Medical Center Goettingen, Georg-August-University Goettingen, Goettingen, Germany, dczesni@gwdg.de

Rachel E. Dew  Division of Child & Adolescent Psychiatry, Department of Psychiatry & Behavioral Sciences, Duke Child & Family Study Center, Duke University Medical Center, Durham, NC, USA, rachel.dew@duke.edu

Molly A. Erickson  Department of Psychological and Brain Sciences, Indiana University, Indianapolis, IN, USA, ericksma@indiana.edu

Yuko Higuchi  Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan, yuko.higuchi@auone.jp
**Toru Ito**  Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan, toru2008@hotmail.co.jp

**Yasuhiro Kawasaki**  Department of Neuropsychiatry, Kanazawa Medical School, Kanazawa, Japan, kawasaki@kanazawa-med.ac.jp

**Eóin Killackey**  Orygen Youth Health Research Centre, Centre for Youth Mental Health, The University of Melbourne, Melbourne, VIC, Australia

**Joachim Klosterkötter**  Department of Psychiatry and Psychotherapy, University Hospital, University of Cologne, Cologne, Germany, joachim.klosterkoetter@uk-koeln.de

**Harold G. Koenig**  Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA, koenig@geri.duke.edu

**Shaheen E. Lakhan**  Global Neuroscience Initiative Foundation (GNIF), Los Angeles, CA, USA, slakhan@gnif.org

**Tania Lecomte**  Department of Psychology, University of Montreal, Montreal, QC, Canada; Fernand-Seguin Research Centre, Louis-H. Lafontaine Hospital, University of Montreal, Montreal, QC, Canada, Tania.lecomte@umontreal.ca

**Vladimir Lerner**  Division of Psychiatry, Ministry of Health, Be’er Sheva Mental Health Center, Be’er Sheva, Israel; Faculty of Health Sciences, Ben-Gurion University of the Negev, Be’er Sheva, Israel, lernervld@yahoo.com; lernerv@bgu.ac.il

**Paul H. Lysaker**  Roudebush VA Medical Center (116h), 1481 west 10th st, IN 46202, USA; Clinical Psychologist, Roudebush VA Medical Center, IN, USA, plysaker@iupui.edu

**Berend Malchow**  Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Georg-August-University Goettingen, Goettingen, Germany, bmalchow@gwdg.de

**Hans-Jürgen Möller**  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, München, Germany, Hans-Juergen.Moeller@med.uni-muenchen.de

**Ann M. Mortimer**  University of Hull, Hull, UK, A.M.Mortimer@hull.ac.uk

**Richard Musil**  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, 80336, München, Germany, Richard.Musil@med.uni-muenchen.de

**Jimmi Nielsen**  Unit for Psychiatric Research, Aalborg Psychiatric Hospital, Aarhus University Hospital, Aarhus, Denmark; Maximum Security Unit, Forensic Psychiatric Department, Region Sjaelland, Denmark, jin@rn.dk
Jennifer A. Nolan  Center for Child and Family Policy, Social Science Research Institute, Duke University, Durham, NC, USA, jennifer.nolan@duke.edu; jan36@cornell.edu

Kieron O’Connor  Fernand-Seguin Research Centre, Louis-H. Lafontaine Hospital, University of Montreal, Montreal, QC, Canada; Department of Psychoeducation and Psychology, University of Quebec in Outaouais, Gatineau, QC, Canada, kieron.oconnor@umontreal.ca

Claire E. Ramsay  Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA, cramsay@emory.edu

Michael Riedel  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, München, Germany; Psychiatric Clinic, Vinzenz-von-Paul-Hospital, Rottweil, Germany, Riedel@med.uni-muenchen.de

Michael S. Ritsner  Department of Psychiatry, Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel; Acute Department, Sha’ar Menashe Mental Health Center, Hadera, Israel, ritsner@sm.health.gov.il; ritsnerm@gmail.com

Stephan Ruhrmann  Department of Psychiatry and Psychotherapy, University Hospital, University of Cologne, Cologne, Germany, stephan.ruhrmann@uk-koeln.de

Rebecca Schennach-Wolff  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, 80336, München, Germany, Rebecca.Schennach-Wolff@med.uni-muenchen.de

Benno Graf Schimmelmann  University Hospital of Child and Adolescent Psychiatry, University of Bern, Bern, Switzerland, benno.schimmelmann@kjp.unibe.ch

Frauke Schultze-Lutter  University Hospital of Child and Adolescent Psychiatry, University of Bern, Bern, Switzerland, frauke.schultze-lutter@kjp.unibe.ch

Florian Seemüller  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, München, Germany, Florian.Seemueller@med.uni-muenchen.de

Ilja Spellmann  Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, München, Germany, Ilja.Spellmann@med.uni-muenchen.de

Tomiki Sumiyoshi  Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan, tomikisumiyoshi840@hotmail.com

Andrew Thompson  Orygen Youth Health, Melbourne Health, North Western Mental Health, Melbourne, VIC, Australia
Karen F. Vieira  Global Neuroscience Initiative Foundation (GNIF), Los Angeles, CA, USA, kvieira@gnif.org

Sasha Whaley  Department of Psychology, Institute of Psychiatry, London, UK, sasha.whaley@kcl.ac.uk

Thomas Wobrock  Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Georg-August-University Goettingen, Goettingen, Germany, twobroc@gwdg.de

Stephen J. Wood  University of Birmingham, Birmingham, UK; Department of Psychiatry, Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Melbourne, VIC, Australia, sjwood@unimelb.edu.au

Til Wykes  Department of Psychology, Institute of Psychiatry, London, UK, til.wykes@kcl.ac.uk
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