BIOGRAPHICAL SKETCH

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NAME: Holt, Daphne J.

eRA COMMONS USER NAME (credential, e.g., agency login): DJHOLT

POSITION TITLE: Associate Professor of Psychiatry

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Brown University; Providence, RiUniversity of Chicago; Chicago, ILUniversity of Chicago; Chicago, ILHarvard Medical School; Boston, MA | B.A.Ph.D.M.D.M.MSc. | 1988199619982004 | BiochemistryNeurobiologyMedicineClinical Investigation |

**NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.**

# A. Personal Statement

Throughout my career, I have studied the neural basis of schizophrenia, initially in post-mortem samples and subsequently using neuroimaging, primarily focusing on a network of regions believed to be involved in the generation of psychotic symptoms— the hippocampus, amygdala, striatum and midline cortical regions. We have investigated these questions using functional and structural neuroimaging in combination with physiology, cognitive neuroscience and clinical assessments. In addition to overseeing the work of my laboratory, I also serve as Co-Director of the Schizophrenia Clinical and Research Program at MGH, which is the psychosis program of the Department of Psychiatry at Massachusetts General Hospital.

# B. Positions and Honors

**Positions and Employment:**

Postdoctoral Training:

1998-2002 Psychiatry Residency, Massachusetts General/McLean Hospital Adult Psychiatry Residency Training Program.

2002-2004 Pfizer Fellow in Clinical Investigation, The Clinical Investigator Training Program, Harvard-MIT Division of Health Sciences and Technology and Beth Israel Deaconess Medical Center.

Academic Appointment:

1992-1996 Visiting Fellow, Harvard University.

* 1. Clinical Fellow in Psychiatry, Harvard Medical School.
	2. Clinical and Research Fellow in Psychiatry, Harvard Medical School.

2004-2006 Instructor in Psychiatry, Harvard Medical School.

2007-2014 Assistant Professor, Harvard Medical School.

2014- Associate Professor, Harvard Medical School.

Hospital Appointment:

* 1. Psychiatry Resident, Massachusetts General and McLean Hospitals.

2002 Administrative Chief Resident, Massachusetts General and McLean Hospitals.

* 1. Clinical and Research Fellow, Massachusetts General Hospital.

2004-2006 Assistant in Psychiatry, Massachusetts General Hospital.

2007-2010 Assistant Psychiatrist, Massachusetts General Hospital.

2010-2016 Associate Psychiatrist, Massachusetts General Hospital.

2016- Psychiatrist, Massachusetts General Hospital.

2004-2012 Associate Director, First-Episode and Early Psychosis Program, Massachusetts General Hospital.

2012-2015 Director of Research, Schizophrenia Clinical and Research Program, Massachusetts General Hospital.

2012- Director, Resilience Enhancement and Prevention Program, Massachusetts General Hospital.

2015- Co-Director, Schizophrenia Clinical and Research Program, Massachusetts General Hospital.

**Other Experience and Professional Memberships:**

1990s-Member of the Society for Neuroscience, American Psychiatric Association, The Cognitive Neuroscience Society.

2009- CNS Spectrums, Editorial Board.

2009- Review Editor, Frontiers in Human Neuroscience.

2012- Psychiatry Journal, Editorial Board

2010, 2011 Ad hoc reviewer for the NIH/BBBP IRG Adult Psychopathology & Disorders of Aging (APDA) Study Section

2012, 2016 Ad hoc reviewer for NIH/BBBP IRG Special Emphasis Panel (SEP) Study Sections

2014, 2015 Reviewer for the MRC

2015, 2016 Reviewer for the American Foundation for Suicide Prevention

**Awards and Honors:**

1988 Magna Cum Laude, Brown University.

1991-1992 The Baxter Foundation MD-PhD Fellowship, University of Chicago.

1993-1996 Individual National Research Service Award.

1996-1998 Training Grant in Growth and Development MD-PhD Fellowship, University of Chicago.

1998 The Daniel X. Freedman Award for outstanding performance in the field of psychiatry, University of Chicago.

2000 The NIMH Outstanding Resident Award.

* 1. The Dupont-Warren Fellowship.
1. The Livingston Award.
2. Janssen Psychiatry Award of Excellence.

2002 Pfizer Psychiatry Resident Award.

1. The Thomas P. Hackett Award, MGH Department of Psychiatry.

2002 The Laughlin Merit Award (Distinguished Laughlin Fellow).

2004 The GlaxoSmithKline Severe Mental Illness Award.

2004 The Rappaport Fellowship in Neuroscience.

2004 Best Abstract, MGH Clinical Research Day.

2004-2006 The Clinical Research Training Program Fellowship, Harvard Medical School.

2006-2009 A 2006, 2007, 2008 & 2009 NARSAD Sidney R. Baer, Jr. Foundation Investigator.

2007 American College of Neuropharmacology Memorial Travel Fellowship.

2009 author of one of the Top 10 cited papers (2006-2008) published in *Schizophrenia Research.*

2011 Associate Member of the American College of Neuropsychopharmacology

# C. Contribution to Science

1. My early work (as a graduate student and resident) focused on understanding the anatomical organization of the human striatum and abnormalities of this structure in schizophrenia. Using immunohistological and mRNA in situ hybridization techniques in post-mortem samples, we showed that the fibers and intrinsic cells of the human striatum are segregated into several anatomical “compartments”, that are similar to (although more complex than) what had been observed in other mammalian species. This compartmentalization of the striatum is akin to the columnar organization of the mammalian cerebral cortex. We found that in the brains of patients with schizophrenia, this organization is altered, with a specific loss of cholinergic interneurons and fibers. Because of the reciprocal functional relationship between dopamine and acetylcholine in the striatum, loss of striatal cholinergic innervation influences brain function and behavior in a manner similar to an excess of striatal dopamine activity. Thus our findings provided evidence for a novel pathophysiological mechanism of the psychotic state.

a. **Holt DJ**, Hersh LB, Saper CB. Cholinergic innervation of the human striatum: a three-compartment model. Neuroscience 1996;74:67-87. PMID: 8843078

b. **Holt DJ**, Graybiel AM, Saper CB. Neurochemical architecture of the human striatum. The Journal of Comparative Neurology 1997;384:1-25. PMID: 9214537

c. **Holt DJ**, Herman MM, Hyde TM, Kleinman JE, Sinton CM, German DC, Hersh LB, Graybiel AM, Saper CB. Evidence for a deficit in cholinergic interneurons in the striatum in schizophrenia. Neuroscience 1999;94:21-31. PMID: 10613493

d. **Holt DJ**, Bachus SE, Hyde TM, Wittie M, Herman MM, Vangel M, Saper CB, Kleinman JE. Reduced density of cholinergic interneurons in the ventral striatum in schizophrenia: an in situ hybridization study. Biological Psychiatry. 2005;58:408-416. PMID: 16023618

2. In 2002, I began to conduct neuroimaging and behavioral studies of patients with schizophrenia, testing the hypothesis that the neurochemical abnormalities leading to psychotic symptoms produce a state of “aberrant salience” in which emotionally neutral information is experienced as salient or threatening. We provided some of the first behavioral and neural evidence for this hypothesis. Moreover, in our fMRI studies, we found that regions involved in salience processing, including the hippocampus, amygdala and medial frontal cortex, were over-responsive to neutral or ambiguous stimuli, as well as to threatening stimuli in certain contexts, in patients with schizophrenia, particularly in those with active delusions. Recently, we have also conducted anatomical studies of this network in schizophrenia and the prodrome, finding evidence for a selective involvement of the CA1 subfield of the hippocampus during the earliest stages of illness, with increasing involvement of other subfields as the disease progresses.

a. **Holt DJ**, Weiss AP, Rauch SL , Wright CI, Zalesak M, Goff DC, Ditman T, Welsh RC, and Heckers S. Sustained activation of the hippocampus in response to fearful faces in schizophrenia. Biological Psychiatry 2005;57:1011-1019. PMID: 15860342

b. **Holt DJ**, Titone D, Long LS, Goff DC, Cather C, Rauch SL, Judge A, and Kuperberg GR. The misattribution of salience in delusional patients with schizophrenia. Schizophrenia Research. 2006;83: 247-256. PMID: 16540291

c. **Holt DJ**, Kunkel L, Weiss AP, Goff DC, Wright CI, Shin LM, Rauch SL, Hootnick J, and Heckers, S. Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. Schizophrenia Research. 2006;82:153-162. PMID: 16377154

d. Ho NF, Iglesias JE, Sum MY, Kuswanto CN, Sitoh YY, De Souza J, Hong Z, Fischl B, Roffman JL, Zhou J, Sim K, **Holt DJ**. Progression from selective to general involvement of hippocampal subfields in schizophrenia. Mol Psych. 2017;1:142-152.

3. After examining the primary networks involved in aberrant salience processing, we have sought to define the responsible mechanism(s). In this work, we have tested the hypothesis that fear inhibition is impaired in psychosis. One form of fear inhibition is fear extinction memory. We reported the first evidence for an impairment in fear extinction memory in schizophrenia. We then linked this impairment to abnormal functioning of the ventromedial prefrontal cortex and an associated network. Currently, we are also examining a second type of fear inhibition in relation to the generalization of learned fear, to determine whether fear inhibition is also deficient during encoding and immediate retrieval of learned fear responses in schizophrenia.

a. **Holt DJ,** Lebron-Milad K, Milad MR, Rauch SL, Pitman RK, Orr SP, Cassidy BS, Walsh JP, Goff DC. Extinction memory is impaired in schizophrenia. Biological Psychiatry 2009;65: 455-63. PMID: 18986648

b. **Holt DJ**, Coombs G, Zeidan MA, Goff DC, Milad MR. Failure of neural responses to safety cues in schizophrenia. Archives of General Psychiatry 2012; 69: 893-903.

c. Linnman C, Coombs G, Goff DC, **Holt DJ**. Lack of insula reactivity to aversive stimuli in schizophrenia. Schiz Res 2013; 143: 150-157.

d. **Holt DJ**, Boeke EA, Wolthusen R, Nasr S, Milad MR, Tootell RBH. A parametric study of fear generalization to faces and non-face objects: relationship to discrimination thresholds. Front Hum Neurosci. 2014; 8: 624.

4. Given that psychotic symptoms are often comprised of distorted experiences or beliefs about the self or other aspects of the social world, we have also investigated whether there are changes in the neural systems supporting social cognition in schizophrenia. We conducted the first fMRI study of social reflection in schizophrenia, identifying abnormalities of the function of the default network. To address the potential contribution of confounds associated with illness chronicity, we have also conducted follow-up studies in related non-ill populations, including first-degree relatives of patients with schizophrenia and individuals with psychosis-like experiences.

a. **Holt DJ**, Cassidy BS, Andrews-Hanna JR, Lee SM, Coombs G, Goff DC, Gabrieli JDE, Moran JM. An anterior-to-posterior shift in midline cortical activity during self-reflection in schizophrenia. Biological Psychiatry. 2011; 69:415-23. PMID: 21144498

b. Brent BK, Coombs G, Keshevan MS, Seidman LJ, Moran JM, **Holt DJ**. Subclinical delusional thinking predicts lateral temporal cortex responses during social reflection. Soc Cog Aff Neurosci. 2014; 9: 273-82.

c. Brent BK, Seidman LJ, Coombs G, Keshevan MS, Moran JM, **Holt DJ**. Neural responses during social reflection in relatives of schizophrenia patients: relationship to subclinical delusions. Schiz Res. 2014; 157: 292-298.

d. Brent BK, Seidman LJ, Thermenos HW, **Holt DJ**, Keshavan MS. Self-disturbances as a possible premorbid indicator of schizophrenia risk: a neurodevelopmental perspective. Schiz Res. 2014; 152: 73-80.

5. Lastly, because of evidence that changes in sensory integration, sensory-affective and sensory-motor processing contribute to abnormalities in salience and social information processing in schizophrenia, we have recently conducted studies of these processes and their relationship(s) to social cognition and behavior. We have found that mid-level integration of lower level information (e.g., the integration of object and motion-related information in peripersonal space) is disrupted in relationship to dimensionally defined social functioning in healthy subjects and in patients with schizophrenia.

a. Yue X, Cassidy BS, Devaney, K, **Holt DJ**, Tootell RBH. Lower level features strongly influence responses in the Fusiform Face Area. Cerebral Cortex. 2011; 21:35-47. PMID: 20375074

b. Yue X, Nasr S, Devaney KJ, **Holt DJ**, Tootell BH. FMRI analysis of contrast polarity processing in face-selective cortex in humans and monkeys. NeuroImage 2013; 76: 57-69.

c. **Holt DJ**, Cassidy BS, Yue X, Rauch SL, Boeke EA, Nasr S, Tootell RBH, Coombs III G. Neural correlates of personal space intrusion. J Neurosci. 2014; 34:4123-34.

d. **Holt DJ**, Boeke EA, Coombs C, DeCross SN, Cassidy BS, Stufflebeam S, Rauch SL, Tootell, RBH. Abnormalities in personal space and parietal-frontal function in schizophrenia. NeuroImage Clin. 2015; 9: 233-43.

**Complete List of Published Work in MyBibliography:** <http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44121203/?sort=date&direction=ascending>

# D. Research Support

**ONGOING**

NIMH RO1MH095904 (Holt)

3/12-12/16 in NCE

The Neural Basis of Deficits in Fear Acquisition and Extinction in Schizophrenia

This 5-year study will investigate the neural underpinnings of abnormalities in fear learning and extinction recall in schizophrenia, and their associations with symptoms and antipsychotic treatment, using multi-modal imaging techniques.

Role: PI.

NIMH RO1MH09793 (Chen)

10/12-09/17

Face Processing Systems in Schizophrenia Spectrum Disorders.

The goal of this 5-year project conducted at McLean Hospital is to test the hypothesis that visual and cognitive deficits contribute to abnormalities in face processing, and the associated deficits in social functioning, in schizophrenia spectrum disorders.

Role: Co-Investigator.

MGH Executive Committee On Research. The Claflin Distinguished Scholar Award (Holt)

7/14-06/16 (1-year NCE)

The Neural Basis of Paranoia: a PET/fMRI Study.

This combined functional MRI/Positron Emission Tomography study will test the hypothesis that abnormal fear learning is linked to dopamine dysregulation (as measured by the D2 dopamine receptor ligand, raclopride) in subsyndromal psychosis.

Role: PI.

NINDS R21NS090169 (Mandeville)

08/15-07/17

PET/MRI Measurements of basal DA function in human subjects.

The goal of this project is to translate a novel method for assessing basal dopamine levels using simultaneous PET and fMRI in healthy human subjects, and then to apply this methodology to study the role of dopamine in chronic pain.

Role: Co-investigator

NIH 1 U01 MH109977 (Shenton, Breier)

05/16-02/21

Human Connectome Project for Early Psychosis

The primary goal of this project is to acquire high quality data that are consistent with that acquired as part of the original Human Connectome Project (HCP). We will thus provide important behavioral, clinical, cognitive, and imaging data, on an important cohort of early psychosis patients, which will be made available to the research community.

Role: Site PI

NIMH 1 RO1MH109562 (Holt)

09/16-08/21

Neural mechanisms of social distance in psychosis

This 5-year project will test the hypothesis that some forms of social dysfunction in psychosis arise from disruption of neural mechanisms governing sensory-motor processing within the space surrounding the body.

Role: PI

Sidney R Baer Jr. Foundation (Holt)

07/16-6/19

Resilience Training on the College Campus - an early intervention program for psychosis spectrum youth.

The goal of this 3 year project aims to test the feasibility, acceptability and efficacy of a brief resilience-enhancing intervention implemented on a college campus for college-aged youth with subsyndromal psychotic symptoms.

Role: PI

**COMPLETE**

NIMH R21MH097094 (Holt, Dickerson)

10/12-9/14

Social Cognitive Impairment in Frontotemporal Degeneration and Schizophrenia.

The goal of this two-year project was to identify the common behavioral and neural features of social cognitive impairment in patients with frontotemporal degeneration and schizophrenia for the overall purpose of developing a uniform battery to test social cognitive function in neuropsychiatric disorders.

Role: Co-PI.