Cognitive Impairment in Major Depressive Disorder

Clinical Relevance, Biological Substrates, and Treatment Opportunities

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Preface

The global economic topography has witnessed a tectonic plate shift toward the "human capital economy." The skillsets required to be an effective participant in the global workforce were previously described as "simple" and "manual," but today are characterized as "complex" and "cognitive." An observation, aligned with the conceptual macroeconomic framework of the Solow–Swan effect, was that the troika of technological advance, productivity, and workplace opportunity are positively correlated. The digital revolution, however, represents an exception to the foregoing correlation insofar as the unprecedented technological capability for automation, lean manufacturing, and efficiency has increased productivity (in some sectors), yet has decreased workplace opportunities.

Economists often refer to the "polarization" of the workforce, referring to the significant reduction of "midlevel" positions and instead a disproportion of job availability for those at the entry level, often low skill and low paying positions, or high skillset positions requiring significant education attainment. The emphasis on the STEMs (Science, Technology, Engineering, and Math) as an asset to increase the probability of entering into higher paying jobs instantiates the relevance of cognitive capability in the global economy. "Cost of illness" and "workplace depression" studies consistently identify depressive disorders as a leading cause of cost and disability globally. Symptom structure analyses indicate that residual cognitive problems are identified by patients as a principal quality of life detractor and barrier to full functional recovery.

It has been recognized for a long time that cognitive dysfunction is an intrinsic aspect of depressive disorders. Notwithstanding, cognitive function in depressive disorders has received relatively less attention than other common and/or severe brain disorders across the developmental trajectory (e.g. bipolar disorder, schizophrenia, autism, dementing disorders). A highly reproducible finding has been that a substantial proportion of adults with depressive disorders have clinically significant deficits across disparate cognitive functions during and between acute episodes. The pertinence of cognitive dysfunction in depression is underscored by the observation that cognitive dysfunction is a critical mediator of adverse psychosocial outcomes as well as work-related disability. For the past several decades, remission of symptoms has been emphasized as the desired therapeutic objective in depressive disorders. Notwithstanding, most individuals with depressive disorders in remission continue to evince prominent psychosocial difficulties. The disconnection between conventional mood symptoms and functional outcome provided the impetus for identifying proximate mediators of functional outcome. Depressive disorders, like most brain disorders, are impairing largely due to the pervasiveness and persistence of cognitive deficits.

The moniker, "Systemically Important Financial Institutions" (SIFIs), a key output of the Dodd-Frank Act (2010), refers to financial organizations that are so critical to the global economic infrastructure that their demise would have catastrophic economic effects globally. Cognition in depressive disorders can also be conceptualized as a SIFI: a "Systemically Important Functional Index." In other words, cognitive function amongst individuals with depressive disorders is "Too Big to Fail" given its centrality to human positive mental health, day-to-day function, and the human capital economy.

This textbook contains contributions from global experts in psychiatry, psychology, primary care, psychometrics, neuroscience, and healthcare policy. The overarching aims of this textbook are: to increase awareness of cognitive dysfunction in major depression; to underscore its impact from clinical and population health perspectives; to review the underlying pathoetiological substrates as well as moderational influences; and to provide practical approaches to assessment, measurement, treatment, and prevention. Across many chronic diseases (e.g. heart disease, diabetes mellitus), optimal health outcomes are achieved by identifying proximate determinants of health outcomes. The evidence indicates that in depressive disorders (as well as most other brain disorders), cognitive function is the critical determinant of health outcome.

It is my hope that this book serves not only as an encyclopedic repository of information but also provides a comprehensive survey of the "cognitive landscape" capturing both the surreal advances that have been made in the field as well as directions for future research. I thank all of the contributors for their enormous effort and commitment to this field. In addition, I want to particularly thank the patients and families I've had the privilege to meet throughout my career who have inspired me and have always reminded me that Osler was correct when he stated, "Listen to your patient, he is telling you the diagnosis."

Dr. Roger S. McIntyre

Abbreviations

3HK: 3-hydroxykynurenine
Aβ: amyloid-beta
AACAP: American Academy of Child and Adolescent Psychiatry
ABCR: action-based cognitive remediation
ABM: attention bias modification
ACC: anterior cingulate cortex
ACGC: Applied Cognition-General Concerns
ACT: alpha(1)-antichymotrypsin
ACTH: adrenocorticotrophic hormone
AD: Alzheimer's disease
ADAS-cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADHD: attention-deficit/hyperactivity disorder
ADL: activities of daily living
AFT: Advanced Finances Task
AIC: anti-inflammatory cytokines
AmNART: American National Adult Reading Test
ANT: Attention Network Task
APA: American Psychiatric Association
AQP4: aquaporin-4
ASRS: Attention Deficit/Hyperactivity Disorder Self-Report Scale
AVLT: Auditory Verbal Learning Test
AVP: vasopressin
BAC: blood alcohol concentration
BASIS: Behavior and Symptom Identification Scale
BBB: blood–brain barrier
BC-CCI: British Columbia Cognitive Complaints Inventory
BD: bipolar disorder
BDI-II: Beck Depression Inventory, 2nd Edition
BDNF: brain-derived neurotrophic factor
BDQ: Brief Disability Questionnaire
BLA: basolateral nucleus
BMI: body mass index
BOLD: blood oxygen level detection
BPI: Brief Pain Index

BRIEF-A: Behavior Rating Inventory of Executive Function
BSAT: Brixton Spatial Anticipation Test
CA: cornu ammonis
CADASIL: cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy
CADSS: Clinician-Administered Dissociative States Scale
CAM: complementary alternative medicine
CAMCOG: Cambridge Cognitive Examination
CAMCOR: Cambridge Cognitive Examination-Revised
cAMP: cyclic adenosine monophosphate
CANTAB: Cambridge Neuropsychological Test Automated Battery
CAT: computerized adaptive testing
CBB: CogState Brief Battery
CBT: cognitive behavioral therapy
CCN: cognitive control network
CDQ: Cognitive Dysfunction Questionnaire
CDR: Cognitive Drug Research
CeA: central nucleus
CEPO: carbamylated erythropoietin
CFS: chronic fatigue syndrome
CGI-I: Clinical Global Impression – Improvement
CGI-S: Clinical Global Impression – Severity
CGS-I/S: Clinical Global Scale – Improvement/Severity
CI: confidence interval
CIAS: Cognitive Impairment Associated with Schizophrenia
CNS: central nervous system
COWAT: Controlled Oral Word Association Test
CPFQ: Cognitive and Physical Functioning Questionnaire
CPT: Continuous Performance Test
CR: cognitive remediation
CREB: cAMP response element-binding protein
CRF: adrenocorticotrophic-releasing factor
CRH: corticotropin-releasing hormone
CRP: C-reactive protein
CRT: Choice Reaction Time
CRT: cognitive remediation therapy
CSF: cerebrospinal fluid
CSH: cognitive speed hypothesis
CT: computerized tomography

CVLT: California Verbal Learning Test
dACC: dorsal anterior cingulate cortex
DBS: deep brain stimulation
DDS: Denver Developmental Screening Test
DEFS: Deficits in Executive Function Scale
DHEA: dehydroepiandrosterone
DLPFC: dorsolateral prefrontal cortex
DLRF: daily living and role functioning
DM2: type II diabetes
DMN: default mode network
dmPFC: dorsomedial prefrontal cortex
DSM: *Diagnostic and Statistical Manual of Mental Disorders*
DSST: Digit Symbol Substitution Test
DST: dexamethasone suppression test
DTI: Diffusion-tensor imaging
DZ: dizygotic
EAAT: excitatory amino acid transporter
ECT: electroconvulsive therapy
EF: executive function
EN: emotion network
EPO: erythropoietin
EPO-R: erythropoietin receptor
ERP: event-related potentials
EWPS: Endicott Work Productivity Scale
FA: fractional anisotropy
FDA: Food and Drug Administration
fMRI: functional magnetic resonance imaging
FPRS: Faces Pain-Rating Scale
GABA: gamma-aminobutyric acid
GFAP: glial fibrillary acidic protein
Glut 1: glucose transporter 1
GM: Gray Matter
GR: glucocorticoid receptor
GSK3β: glycogen synthase kinase 3 beta
HAM-D: Hamilton Psychiatric Rating Scale for Depression
HC: healthy control
HC: hippocampal
HIF: hypoxia inducible factor
HOMA-IR: Homeostatic Model Assessment – Insulin Resistance

HPA: hypothalamic–pituitary–adrenal
HR: hazard ratio
IAPS: International Affective Picture System
IBS: irritable bowel syndrome
IC: insular cortex
ICD: International Classification of Diseases
IFNγ: interferon-Gamma
IGF-1: insulin-like growth factor 1
IGT: Iowa Gambling Task
IL: interleukin
ILF: inferior longitudinal fasciculus
IMDCP: International Mood Disorders Collaborative Project
IPT: interpersonal psychotherapy
IQ: intelligence quotient
IR: insulin resistance
IS: imperative signal
ISH: *in situ* hybridization
IU: international unit
JAK: janus kinase
JNK: C-jun N-terminal kinases
LIFE-RIFT: Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning Tool
LTD: long-term depression
LTP: long-term potentiation
MADRS: Montgomery–Åsberg Depression Rating Scale
MAO-A: monoamine oxidase A
MAPK: mitogen-activated protein kinase
MCCB: MATRICS Consensus Cognitive Battery
MCI: mild cognitive impairment
MD: mean difference
MDD: major depressive disorder
MDE: major depressive episode
MDPU: Mood Disorders Psychopharmacology Unit
MMSE: Mini Mental Status Exam
MNS: mirror neural system
MoCA: Montreal Cognitive Assessment
MOS-Cog: Medical Outcomes Study Cognitive Functioning Scale
MPFC: medial prefrontal cortex
MR: mineralocorticoid receptor

MRI: magnetic resonance imaging
MS: multiple sclerosis
MSIF: Multidimensional Scale of Independent Functioning
MZ: monozygotic
NAA: *N*-acetylaspartate
NAcc: nucleus accumbens
NART: National Adult Reading Test
NCS-R: National Comorbidity Survey Replication
NEAR: Neuropsychological and Educational Approach to Remediation
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NIMH: National Institute of Mental Health
NMDA: *N*-methyl-D-aspartate
NTB: Neuropsychological Test Battery
OCD: obsessive-compulsive disorder
ODD: oppositional defiant disorder
OFC: orbitofrontal cortex
OR: odds ratio
PA: physical activity
PCC: posterior cingulate cortex
PDQ: Perceived Deficits Questionnaire
PET: positron emission tomography
PFC: prefrontal cortex
PHQ: Patient Health Questionnaire
PI3K: phosphoinositide 3-kinase
PICs: pro-inflammatory cytokines
PKB: protein kinase B
PRMQ: Prospective and Retrospective Memory Questionnaire
PROMIS: Patient Reported Outcome Measurement Information System
PST: prednisolone suppression test
QA: quinolinic acid
QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Report
Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire
rACC: rostral anterior cingulate cortex
RAVLT: Rey Auditory Verbal Learning Test
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCI: Reliable Change Index
RCT: randomized controlled trial
RDoC: Research Domain Criteria
RNA: ribonucleic acid

ROS: reactive oxygen species
RR: relative risk
rs-fMRI: resting state functional magnetic resonance imaging
RSO: relation to self and others
rTMS: repetitive transcranial magnetic stimulation
SAME: S-adenosyl methionine
SCG: subgenual cingulate cortex
SCL-90: Symptom Checklist-90
SD: standard deviation
SDS: Sheehan Disability Scale
SE: standard error
SF-12: 12-item Short Form Health Survey
SGAC: subgenual anterior cingulate cortex
SLF: superior longitudinal fasciculus
SMD: standardized mean difference
SMILE: Standard Medical Interventions and Longterm Exercise
SN: salience network
SNPs: single-nucleotide polymorphisms
SNRI: serotonin-norepinephrine reuptake inhibitor
SPC: superior parietal cortex
SRE: self-reference effect
SRT: Simple Reaction Time
SSPA: Social Skills Performance Assessment
SSPG: steady state plasma glucose
SSRI: selective serotonin reuptake inhibitor
STAR*D: Sequenced Treatment Alternatives to Relieve Depression
STAT: signal transducer and activation of transcription
TAK-1: transforming growth factor β-activated kinase 1
TBRI: to be remembered item
tDCS: transcranial direct current stimulation
TGF-β: transforming growth factor beta
TMT: Trail Making Test
TNF: tumor necrosis factor
TNFR: tumor necrosis factor receptor
ToM: theory of mind
TRD: treatment-resistant depression
TrkB: tyrosine kinase receptor B
TSR: threat of social rejection
UPSA: University of California San Diego Performance-Based Skills Assessment

VBM: voxel-based morphometry
VEGF: vascular endothelial growth factor
VFT: Verbal Fluency Test
VLPFC: ventrolateral prefrontal cortex
WAIS: Wechsler Adult Intelligence Scale
WCST: Wisconsin Card Sorting Test
WHO: World Health Organization
WHS: World Health Survey
WISC-III: Wechsler Intelligence Scale for Children-Third Edition
WLQ: Work Limitations Questionnaire
WM: white matter
WM: working memory
WMD: weighted mean difference
WMH: white matter hyperintensities
WMS: Wechsler Memory Scale
WPAI: Work Productivity and Activity Impairment
YoE: years of education