THE WILEY HANDBOOK ON THE

AGING MIND AND BRAIN

EDITED BY

MATTHEW RIZZO · STEVEN ANDERSON
BERND FRITZSCH

WILEY Blackwell

The Wiley Handbook on the Aging Mind and Brain

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The result of everyone's efforts is a collective examination of the major theoretical, empirical, and practical issues related to the aging mind and brain. We have provided an overview of the field, covering issues on the cusps between theory and practice. Major sections of the book address theory, animal models; social and humanistic perspectives; methods of assessment; brain functions and behavior across the lifespan; brain disease and dysfunction; optimizing brain function in health and disease; and legal and ethical issues. Topics span psychology, cognitive neuroscience, physiology, biology, neuroimaging, computer science, human factors and ergonomics, human systems integration, medicine, nursing, social work, ethics, law, humanities, and public policy. We conclude with ideas on potential opportunities to advance mind and brain health over the coming decades. Potential audiences include researchers and practitioners interested in aging and cognition, state and federal administrators wanting to fund relevant research and programs, and public health officials charged with decisions on funding research and healthcare projects and systems at the state and national levels.

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List of Abbreviations

Aβ "A-beta" peptide, a component of amyloid plaques
ACA Anterior cerebral artery
ACO Accountable Care Organizations
AD Alzheimer's disease
ADC Apparent diffusion coefficient
ADNI Alzheimer's Disease Neuroimaging Initiative
AGS American Geriatrics Society
AHA/ASA American Heart Association/American Stroke Association
AICA Anterior inferior cerebellar artery
ALF Assisted living facility
ALS Amyotrophic lateral sclerosis
ABM Aging brain model
ADR Acute dystonic reactions
ALW Assisted Living Workgroup
AMD Age-related macular degeneration
AMDA American Medical Directors' Association
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Anti-VEGF Anti vascular endothelial growth factor
AoA Administration on Aging
APOE Apolipoprotein E
APOε Apolipoprotein E epsilon
APP Amyloid precursor protein
ASL Arterial spin labeling
ATD Ascending tract of Deiters
ATP Adenosine triphosphate

BCI Brain–computer interface
BF Basal forebrain
BGDs Balance and gait disorders; they limit mobility and are a major cause of disability
BDNF Brain-derived neurotrophic factor
BI Barthel Index
BINT Blast-induced neurotrauma
BOLD Blood oxygen level dependency
BoNT Botulinum toxin
BP Blood pressure

BPPV Benign paroxysmal positional vertigo
BVL Bilateral vestibular loss

CAA Cerebral amyloid angiopathy
CAD Computer aided design
CADASIL Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAM Computer aided manufacturing
CARASIL Cerebral autosomal recessive arteriopathy with subcortical infarct and Leukoencephalopathy
CBD Corticobasal degeneration
CBF Cerebral blood flow
CBS Corticobasal syndrome
CC Corpus callosum
CCH Cognitive control hypothesis
CCR Cervicocollic reflex
CDC Centers for Disease Control and Prevention
CDE Common data element
Cdh23 Cadherin 23
CEA Carotid endarterectomy
CHA2Ds score One point each for congestive heart failure, hypertension, age ≥75 years and diabetes mellitus, and two points for stroke or TIA
CHA_2DS_2–VASc score One point each for congestive heart failure, hypertension, age 65–74years, diabetes mellitus, vascular disease, female sex/gender. Two points each for age ≥ 75 years and stroke or TIA
Cho Choline
Cis Cochlear implants
CMMI Center for Medicare and Medicaid Innovation
CMS Center for Medicare and Medicaid Services
CNS Central nervous system
CPG Central pattern generator, typically referring to a spinal motor control center
CPP Cerebral perfusion pressure
Cr Creatine
CREATE Center for Research and Education on Aging and Technology Enhancement
CROS Contralateral routing of sound
CSF Cerebrospinal fluid
CT Computed tomography
CTE Chronic traumatic encephalopathy
CTE-MND Chronic traumatic encephalopathy-motor neuron disease

DAI Diffuse axonal injury
DBS Deep brain stimulation
DET Differential emotions theory
DHHS Department of Health and Human Services
DLB Dementia with Lewy Bodies
DMN Default mode network
DoD/VA US Department of Defense and Veterans Administration
DP *dementia pugilistica*
DRBA Dopamine receptor blocking agents
DRD Dopa responsive dystonia
DTI Diffusion tensor imaging

DVN Descending vestibular nucleus
DWI Diffusion weighted MRI

EF Executive functions
EHs Eye-head neurons, VN neurons projecting to EOM motoneurons
eIF2α Eukaryotic Translation Initiation Factor 2α
ELLP Extremely long-lived proteins
EOMs Extra-ocular muscles, six muscles responsible for eye movement
ER Endoplasmic reticulum
ET Essential tremor
ETC Electron transport chain

FA Fractional anisotropy
FDA US Food and Drug Administration
FDG-PET Fluorodeoxyglucose – positron emission tomography
FES Functional electrical stimulation
FLH Frontal lobe hypothesis
FMD Functional movement disorders
fMRI functional magnetic resonance imaging
FTD Frontotemporal dementia
FTDP Frontotemporal dementia with parkinsonism
FTLD Frontotemporal lobar degeneration
FTNs Floccular target neurons, VN neurons that are inhibited by floccular Purkinje cells

GABA γ-aminobutyric acid, an inhibitory transmitter of the mammalian CNS
GAO Government Accountability Office
GDNF Glial cell-derived neurotrophic factor
Glu Glutamate
GPC Glycerophosphocholine
GPE Glycerophosphoethanolamine
GPi Globus pallidum interna
GRE Gradient recalled echo

HAROLD Hemispheric asymmetry reduction in older adults
HCBS Home and community based services
HD Huntington's disease
HFE Human factors engineering

ICD International Classification of Diseases
ICP Intracranial pressure
IHCs Inner hair cells
INR International normalized ratio
IOM Institute of Medicine
IPAE Integrated perspective of aging and emotion

LA Leukoaraiosis
Lac Lactate
LADIS Leukoaraiosis and disability study
LPR Line of polarity reversal
LTC Lifespan theory of control
LVN Lateral vestibular nucleus
LVST Lateral vestibulo-spinal tract, originates in the LVN

MAO Monoamine oxidase
MCA Middle cerebral artery
MCI Mild cognitive impairment
MCR Motoric cognitive risk syndrome
MD Mean diffusivity
MELAS Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
mI Myo-Inositol
MLF Medial longitudinal fascicle
MLR mesencephalic locomotor region
MRI Magnetic resonance imaging
MRS MR spectroscopy
mRS Modified Rankin Scale
MSA Multiple system atrophy
MSSP Medicare Shared Savings Plan
MSTd Dorsal aspect of the medial superior temporal gyrus
mTBI Mild traumatic brain injury, aka concussion
mTOR Mechanistic target of rapamycin
MVN Medial vestibular nucleus
MVST Medial vestibulo-spinal tract

NAA N-acetyl aspartate
NAPA National Alzheimer's Project Act
NEI-VFQ National Institute Visual Function Questionnaire
NFCSP National Family Caregiver Support Program

NFL National Football League
NFT Neurofibrillary tangle
NGF Nerve growth factor
NHRA Nursing Home Reform Act
NIH National Institutes of Health
NIHSS National Institutes of Health Stroke Scale
NINCDS/ADRDA National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association (ADRDA)
NINDS-AIREN National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NLRP3 NACHT, LRR and PYD domains-containing protein 3
NMDA N-methyl-D-aspartate receptor for the transmitter glutamate
NPH Normal pressure hydrocephalus

OAA Older Americans Act
OCR Ocular counter-rolling
OHCs Outer hair cells
OIG Office of Inspector General
OKN Opto-kinetic nystagmus

PC Phosphocholine
PCA Posterior cerebral artery
PCP Planar cell polarity
PCS Post concussion syndrome
PD Parkinson's disease
PPD Dementia in Parkinson's disease
PE Phosphoethanolamine

PET Positron emission tomography
PFC Prefrontal cortex
PHF Paired-helical filament
PICA Posterior inferior cerebellar artery
PINK1 PTEN-induced putative kinase 1
PIVC Posterior insular vestibular cortex
PPN Pedunculopontine nucleus
PRISM Personal Reminder Information and Social Management
PSP Progressive supranuclear palsy
PTSD Post-traumatic stress disorder
PSP Progressive supranuclear palsy
PVPs Position-vestibular-pause neurons, neurons of the VOR

RBD REM sleep behavior disorder
RD Radial diffusivity
REM Rapid eye movement
RNS Reactive nitrogen species
ROS Reactive oxygen species
RPE Retinal pigment epithelium
ROI Region of interest
ROS Reactive oxygen species
RSFC Resting-state functional connectivity
RSNs Resting state networks
rt-PA Recombinant tissue plasminogen activator

SABG Senescence-associated β-galactosidase
SAVI Strength and Vulnerability Integration model
SGNs Spiral ganglion neurons
sICH Symptomatic intracerebral hemorrhage
SjvO2 Jugular bulb venous oxygen saturation
SN Substantia nigra
SNP Special Needs Plan
SOC Selective Optimization with Compensation Model
SOCER Selective Optimization with Compensation – Emotion Regulation Model
SPS3 Secondary Prevention of Small Subcortical Stroke–3
SSNHL Unilateral sudden sensorineural hearing loss
SSRIs Selective serotonin reuptake inhibitors
SST Socioemotional Selectivity Theory
STN Subthalamic nucleus
SWI Susceptibility-weighted imaging

TIA Transient ischemic attack/stroke
TBI Traumatic brain injury
TBM Tensor based morphometry
ToM Theory of Mind

USPTF United States Preventive Services Task Force

VBM Voxel-based morphometry
VCI Vascular cognitive impairment

VCR Vestibulo-collic reflex
VIP Ventral intraparietal
VOR Vestibulo-ocular reflex (AVOR = angular VOR; TVOR = translational VOR)
VSR Vestibulo-spinal reflex
VN Vestibular nucleus/nuclei
VO Vestibular-only (or non-eye movement) neurons, project to spinal cord and thalamus

WHO World Health Organization
WM Working memory

Glossary

ABCD2 score – This is a score to stratify the immediate stroke risk in patients who had TIA. One point each is given for age >60 years, BP >140/90, dysarthria, diabetes mellitus, and symptom duration of 10–60 minutes. Two points are given if the patient has weakness or the symptom duration lasts over 60 minutes. No point is given for symptom duration of less than 10 minutes. The maximum total points are 7. Based on the total score, patients are grouped as low risk (0–3), moderate risk (4–5) and high risk (6–7).

Accelerometer – A sensor that measures acceleration of itself and moving objects to which it is affixed (such as a person's body), generally with respect to the Earth's gravitational field. Accelerometers are commonly embedded in personal devices such as smartphones and watches and used to track outcomes such as activity, energy, and expenditure, and to infer physical inactivity and sleep.

Active Aging – Participation in social, economic, cultural, spiritual and civic affairs, not just the ability to be physically active or participate in the labour force (WHO, 2002).

Activities of Daily Living (ADL) – Basic self-care tasks and skills, including feeding, toileting, grooming, bathing, and transferring (such as moving from bed to wheelchair).

Acute Ischemic Stroke – Refers to infarction of an area of the brain due to absent or decreased blood flow from an occluded or stenotic artery supplying it. Patients present with sudden onset of focal neurological deficit. The type of neurological symptoms experienced depends on the area of the brain affected by a particular artery.

Age Discrimination in Employment Act of 1967 (ADEA) – A federal law designed to protect both employees and job applicants 40 years of age or older from employment discrimination based on age.

Age Studies – An interdisciplinary field of study that explores the individualized experience of age, aging, older age, and intergenerational relationships. Age Studies employs the methods and materials of the creative arts and humanities and often emphasizes methodologies that are not primarily quantitative or clinical.

age-1 – Gene tied to fertility that has been shown to extend lifespan.

Ageism – Prejudice or discrimination on the basis of a person's age, i.e., older people or youth, which can be perpetrated in multiple contexts and on interpersonal, institutional, and systemic levels.

Aggregated National Cost of Dementia – An attempt to project future cost of dementia caretaking from extrapolating past costs to future expected increases in demented patients as populations age and have an increased prevalence of dementia. The current cost of dementia was estimated around $200 billion in 2015 and is projected to reach over $1 trillion in 2050.

Aging – A multidimensional accumulation of changes over time that decreases the ability of the organism to withstand extrinsic stresses and is an independent risk factor for neurodegenerative disease and death.

Akathisia – Restless movements, usually with inner urge.

Akinesia – Lack of movements.

Alpha – Oscillatory neural activity observed in the 812 Hz spectral frequency range.

Alpha-Synuclein – A protein normally found in normal tissues, whose clear function is not yet known.

α-Synuclein – Gene encoding a presynaptic protein involved in cellular trafficking that is implicated in Parkinson's disease.

ALS – Amyotrophic lateral sclerosis; a neurodegenerative disease leading to loss of motor neurons.

Alzheimer's disease – A progressive human brain disease that slowly impairs cognitive abilities and culminates in a state of dementia, and is associated with ß-amyloid protein plaques and neurofibrillary tangles composed of tau protein aggregates.

Amyloid – Protein fragments that are produced in healthy people but can aggregate in human disease.

Anhedonia – The inability to enjoy or derive pleasure from things that would typically be pleasurable for the individual.

Anomia – The inability to name things despite some understanding of what they are.

Anorgasmia – Inability to achieve an orgasm due to psychological factors, vascular dysfunction, peripheral nervous system lesions, or CNS lesions affecting the spinal cord or cerebrum.

Anosognosia – The inability to recognize one's own neurologic deficits.

Antagonistic Pleiotropy – The idea that aging exists because traits that are beneficial to the organism's fitness and detrimental to somatic maintenance and prolonged survival.

Antipsychotics – Drugs used against psychosis.

Anxiety Disorder, Generalized – Excessive worry about general daily events causing anxiety lasting for at least six months.

Anxiety Disorders – Conditions producing fear and physical symptoms, such as sweating, dizziness and trembling, without any real source of fear, which interferes with daily functioning and relationships.

Aphasia – An abnormality of language where the individual is unable to produce and/or understand language.

Assisted Living – A type of residential care that provides personal care for individuals who need assistance with activity of daily.

Astereognosis – The inability to recognize an object by touch despite intact sensation.

Asterixis – Negative myoclonus, brief loss of contraction.

Astrocytes – Supporting cells of the brain, also help in neuronal metabolism.

Ataxia – An abnormality of coordination that affects voluntary movements, including limb and axial movements and gait.

Auditory System – This term is used for the entire middle ear, cochlear and spiral ganglion parts of the inner ear, as well as the brainstem auditory nuclei (ventral and dorsal cochlear nuclei, superior olive complex), midbrain (inferior colliculus), diencephalon (medial geniculate body), and various primary and secondary auditory cortex areas of the temporal lobe.

Automated Static Perimetry – Commonly used diagnostic tests for evaluation of the visual field in disease conditions affecting the afferent visual pathway. These techniques use computerized algorithms to determine the minimal threshold for stimulus detection at predetermined locations of the visual field. The clinical significance is determined by comparing subject threshold values to those of matched normal controls.

Autonomy – The capacity for self-determination and independence, which often is threatened as the brain ages, and particularly in the context of age-related brain disorders.

Axonal Injury – Refers to stretching or distraction of nerve cell filaments caused by unequal forces acting on different parts of the brain. Important stress points include the interface between the gray matter of the cortical mantle and the underlying white matter, the splenium of the corpus callosum, and areas of the brainstem. In such regions, rotational or translational forces may stretch or snap nerve cell filaments. Such forces may arise with rapid accelerations and decelerations of the head, as in a car crash or a fall. In theory, a cascade of associated biochemical event begins at the time of injury, which can cause further injury and affect other areas of the brain.

Baby Boomers – People born during the post-World War II "baby boom," approximately between 1946 and 1964.

Balance – The ability of keeping an upright position while standing or moving around and doing so against perturbations. Three sensory inputs (vestibular, proprioception, vision) provide the chief input that results in proper motor output to maintain the desired posture.

Barthel Index (BI) – The BI is a functional outcome scale. It assesses the main ten activities of daily living: feeding, bathing, grooming, dressing, bowel, bladder, toilet use, transfers, mobility, and use of stairs. A score is given for each of the activities of the daily living, and the final total score ranges from 0 to 100 with 100 being completely independent. It is commonly used in rehabilitation centers to assess outcomes following physical and occupational therapy.

Basal Ganglia – A group of subcortical nuclei (caudate, putamen, globus pallidus, substantia nigra, pars compacta, subthalamic nucleus, ventral striatum).

BDNF – Brain-derived neurotrophic factor; a growth factor that stimulates neurite growth.

Behavioral and Psychological Symptoms of Dementia (BPSD) – Distressing non-cognitive symptoms of dementia, such as agitation, aggressive behavior, wandering, and resistance to care.

Biomarker – A measureable quantity whose presence is associated with a pathophysiologic process affecting an organism.

Bipolar Disorder – A chronic condition that involves periods of mania and sometimes depression. It interferes with daily functioning and relationships.

Blood Oxygenation Level Dependent (BOLD) Imaging – Standard technique to generate images in functional MRI (fMRI) studies, which relies on regional differences in oxyhemoglobin content in the blood to delineate regional cerebral activity.

Bradykinesia – Decreased speed of movements.

Brain–Computer Interface (BCI) – The use of computer technology linked to some aspect of brain physiology to enhance perception, movement or cognition.

Brinley Plots – Analysis method where reaction times of older adults are plotted as a function of the reaction times of younger adults. If a single linear regression function significantly predicts the relationship between the group RTs, generalized slowing is said to account for the observed result.

Capacity – The presence of capabilities needed to be able to adequately manage activities in question.

Cardiorespiratory Fitness (CRF) – A health-related component of physical fitness that relates to the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and to eliminate fatigue products after supplying oxygen (Caspersen, Powell et al., 1985).

Center for Research and Education on Aging and Technology Enhancement (CREATE) – CREATE is a multidisciplinary, multisite center funded by the National Institute on Aging (a division of the National Institutes of Health) that focuses on older adults' interactions with technology systems.

Cerebral Amyloid Angiopathy (CAA) – CAA refers to the deposition of β-amyloid protein in the walls of penetrating small- to medium-sized arteries, arterioles, and capillaries in the cerebral cortex, leptomeninges, and cerebellum. The β-amyloid proteins infiltrate the media and adventitia, replacing the smooth muscles in the small vessels. Aβ40 deposits are predominantly seen in CAA. With Congo red staining, green birefringence is seen in the polarized light.

Cerebral Blood Flow (CBF) – The amount of blood that flows through the network of cerebral arteries and veins in a given period of time, typically indexed in units of mL/min/100 mL of tissue.

$CHADS_2$ Score – A score ranging from 0 to 6 to stratify the stroke risk in patients with nonvalvular atrial fibrillation. One point each is given for presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and 2 points for stroke or TIA. Anticoagulation is indicated for patients with atrial fibrillation and a score of ≥ 2. If a patient has a score of 0 or 1, further risk stratification for stroke with a CHA_2DS_2–VASc score could be considered. In this measure, one point each is given for congestive heart failure, hypertension, age 65-74 years, diabetes mellitus, vascular disease, and female sex/gender. Two points each are given for age ≥ 75 years and stroke or TIA. CHA_2DS_2–VASc scores range from 0-9.

Cheyne-Stokes Breathing – A breathing pattern characterized by rhythmic waxing and waning of the depth of respiration followed by periods of apnea, often seen in patients with damage to respiratory centers in the brain or congestive heart failure.

Cholinergic – Neurons that use acetylcholine as a neurotransmitter.

Chronic Traumatic Encephalopathy (CTE) – Refers to a distinct pattern of autopsy findings in the brains of individuals who had a reported history of concussive head trauma, generally repetitive, and a range of cognitive, behavioral and personality changes with onset months or even years after last concussion. CTE is broadly related to *dementia pugilistica* or "punch drunk" syndrome first observed in career boxers.

Circumduction – An abnormal lateral swinging motion of an extended or spastic leg.

Classic Test Theory (CTT) – A family of psychometric statistics that evaluates the reliability and validity of a measure by focusing on the overall scale score derived from a specific sample.

It assumes that item responses reflect both the true score and the error score, and that the latter is random. All questions are assumed to be parallel and should be equally weighted. Therefore, every scale score of 10 is equal to every other scale score of 10, regardless of the many ways that item responses sum to a scale score of 10.

clk-1 – Gene encoding an enzyme thought to be involved in regulation of the biological clock.

Clonazepam – A long-acting benzodiazepine medication.

Cognitive Enhancement – Efforts to improve upon normal cognitive abilities (as opposed to treating impaired abilities), typically by pharmacological means, but also including cognitive and behavioral interventions.

Competency – The legal term referring to presumed ability to adequately manage one's affairs. All individuals have this legal status unless determined by the court to not have their capacities.

Computer Aided Design (CAD) – CAD involves the use of computer technology and software for design and design documentation. It replaces manual drafting.

Computer Aided Manufacturing (CAM) – CAM involves the use of computer software and machinery to facilitate and automate manufacturing processes.

COMT – Catechol-o-methyl transferase is an enzyme that metabolizes dopamine and other amines.

Concussion – From Latin "concussus," a shaking. A group of symptoms and signs that begin in the immediate aftermath of a head injury. These may include confusion, loss or clouding of memory, blurry vision, headache, neck pain, dizziness, as well as changes in mood, insomnia, lassitude, and a variety of other complaints. Loss of consciousness is not required for the diagnosis of concussion.

Confusion – A general term for any mental state where the individual responds inappropriately. A state of being uncertain, disoriented, or bewildered.

Conservator – The legal status of a person charged with responsibility for managing the financial affairs, including financial decisions, for an individual lacking capacity to manage their own financial affairs, based on determination by a judge.

Contractual Capacity – Making contracts. Includes (a) ability to understand the nature of the contract being entered into, and (b) the effects of the contract or business agreement (potential risks and benefits).

Cortical Sensory Deficit – A higher level sensory abnormality, such as astereognosia or agraphesthesia, that occurs as a result of injury to the sensory cortex of the brain.

Cortical Visual Impairment – Visual impairment secondary to neurological lesions affecting the visual part of the brain. The ocular structures are either intact, or the abnormalities are insufficient to account for the extent of visual impairment. Cortical visual impairment is also referred to as "cortical blindness," a misleading term, as the visual impairment may not be complete.

CuZnSOD – Cu/Zn superoxide dismutase, an enzyme that protects cells by inhibiting oxidation. When mutated, may cause familial ALS.

Declarative Memory – Memory for facts and events.

Defecography – A method used to identify patients with rectal prolapse, poor rectal evacuation, or megarectum.

Delirium – An acute (hours to days) onset disturbance of the level and content of consciousness, often accompanied by disruption of the sleep-wakefulness cycle, psychomotor hyperactivity or hypoactivity, illusions and visual hallucinations, and emotional lability. The condition typically

fluctuates during the course of the day, is not better explained by a pre-existing baseline dementia, and can be attributed to a general medical condition.

Delta – Oscillatory neural activity observed in spectral frequencies less than 4 Hz.

Delusion – An abnormal, irrational, fixed, false belief or judgment, despite incontrovertible evidence.

Delusional Disorder – Chronic condition producing delusions that interfere with daily functioning and relationships.

Dementia – An usually chronic disturbance of cognition that generally involves more than one cognitive domain (i.e., memory, executive function, visuospatial/perceptive skills, praxis, language, personality/behavior), interferes with a patient's independence at work or other everyday activities, represents a decline compared to patient's baseline performance, and cannot be explained by delirium or a psychiatric disorder (i.e., major depressive disorder, schizophrenia).

Depression – Internal emotional state marked by an abnormal amount of sadness, loss of interest in pleasurable activities. Symptoms including low mood, irritability, loss of interest in pleasurable activities, change in appetite, feelings of worthlessness or excessive guilt, insomnia or hypersomnia, diminished concentration, psychomotor agitation or retardation, loss of energy, and recurrent thoughts of suicide. Depression may be the result of a major depressive disorder. It is also associated with neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease, vascular disease, brain injury, drug effects, other medical disorders, and related psychosocial stress.

Depression, Subsyndromal – Depression resulting in two or more symptoms of major depressive disorder but without depressed mood or loss of interest in pleasurable activities.

Desynchronization – Changes in oscillatory properties of given neuronal populations by either (1) decrease in coherence of oscillatory neural activity within a specific frequency range, or (2) relative decrease in the proportion of units in a neuronal population active in specific frequency range. Quantified by relative decreases in spectral power.

Diagnostic Criteria – A list of clinical criteria that must be met in order for a diagnostic classification to be established.

Diffusion Tensor Imaging (DTI) – MRI-based neuroimaging technique that makes it possible to estimate the location, orientation, and anisotropy of the brain's white matter tracts.

Diminished Capacity – A clinical judgment that ability to perform specified real-life activities (e.g., complex decision-making regarding one's affairs) has been reduced to the point that the individual cannot perform the activities at an adequate level.

Disaggregated Data – Quantitative or qualitative data that has been collected and compiled into summary data, i.e., for use in reporting or analysis, and then broken down into smaller subsets of data.

Donative Capacity – The capacity to decide to make gifts of one's property to others.

Dopamine – A chemical neurotransmitter, mainly used by basal ganglia neurons and prefrontal cortex.

Dysarthria – Slurring of speech.

Dysguesia – An abnormal or impaired sense of taste.

Dyskinesia – Abnormal, involuntary movements, as in Parkinson's disease, which can affect axial and limb muscles.

Dysphagia – Difficulty swallowing.

Dysphonia – Altered voice (soft, low pitched).

Ecological Model – A conceptual model that identifies categories and hierarchies of behavioral influences to help guide the development of public health interventions.

EEG – Electroencephalography, a method with high temporal resolution designed to measure the changes in electric fields generated by populations of post-synaptic potentials of cortical neurons.

Emotion – Brief episodes of complex psychological and physiological states involving coordinated autonomic, hormonal, behavioral and experiential changes, enabling individuals to quickly detect, evaluate, and respond to internal and external stimuli that may significantly change homeostasis.

Emotion Regulation – The processes by which individuals influence which emotions and when emotions occur or not, and how the emotions are experienced and expressed (e.g., intensity, duration, behavioral expression).

Emotional Well-Being – Typically defined as happiness, life satisfaction, or the balance between positive and negative affect.

Encephalopathy – A general term for any disorder of the brain. Often used to describe a syndrome of acute (hours to days) or subacute (days to weeks) onset diffuse brain failure manifested by a reduced level of consciousness (from clouding to coma) and, except when the patient is comatose, also an altered content of consciousness (language and behavior).

Equal Employment Opportunity Commission (EEOC) – The federal agency responsible for enforcing anti-discrimination and anti-retaliation laws in the employment context, including laws against retaliation for protected activities, or discrimination based on a person's race, color, religion, sex (including pregnancy and gender identity), equal pay/compensation, harassment (including sexual harassment), national origin, age (40+), disability, or genetic information.

Erectile Dysfunction (ED) – Inability to achieve or maintain an erection sufficient to permit sexual intercourse. Risk factors include tobacco, alcohol and illicit drug use, diabetes, vascular disease, hypertension, cancer or chemotherapy, infection, spinal cord lesions, neurological conditions, and penile curvature or pain.

ERP – Event-related potentials, a method for measuring changes in stimulus-evoked neural activity by averaging multiple EEG waveforms time-locked to task-related events.

Ethology – The study of humans or animals behaving and interacting in natural settings, as pioneered by the Nobel Laureates Konrad Lorenz, Nikolaas Tinbergen, and Karl von Frisch.

Event-Related Potentials (ERPs) – Experimental methodology that measures small fluctuations in voltage potential across the scalp.

Executive Functions (EF) – An array of relatively unique human integrative cognitive capacities serving goal-oriented and self-regulatory behavior.

Exercise – A subset of physical activity that is planned, structured, and repetitive and performed for the maintenance and/or improvement of physical fitness (Caspersen, Powell, et al., 1985).

Experience Sampling Method (ESM) – Tools and strategies that attempt to validly describe variations in self-reports of mental processes and behavior in real world settings over time. ESM provides data on frequency, patterns and intensity of daily activity, social interaction, movement, psychological processes, thoughts, and thought disturbance. ESM can be applied to study the experience of aging.

Financial Capacity – The capacity to adequately manage the full array of financial activities, including managing funds, creating a will, and entering into contracts.

Fine Motor Task or Skill – Coordination of movements of the hand and fingers with a goal to manipulate small objects in a targeted manner.

Fludeoxyglucose F18 ([^{18}F]fluorodeoxglucose or FDG) – A glucose analogue labeled with the positron-emitting radionuclide fluorine-18 used in PET studies, and whose metabolism runs in parallel with cerebral glucose metabolism.

Frontotemporal Dementia, Behavioral Variant – When damage to frontal or temporal lobes of the brain results in socially inappropriate responses or activities.

Gamma – Oscillatory neural activity observed in spectral frequencies greater than 40 Hz.

Generation X – The generation born after that of the "Baby Boomers," generally between the early 1960s to early 1980s.

Generation Y – Also called Millennials, this cohort follows Generation X, tends to comprise children of Baby Boomers, and first began to reach adulthood at or around the turn of this century (2000).

Generativity – Interest in contributing to the development and well-being of others, such as younger generations and society (Erikson 1982, McAdams and de St. Aubin 1992).

Genomic Instability – High mutational rate that can be a consequence of many mechanisms that have to do with DNA replication, repair, transposition etc.

GIS – A geographic information system designed to capture, store, manipulate, analyze, manage, and display environmental, cultural, or geospatial data. GPS data can be linked to GIS to provide context of a specific person in a given place and time, such as a driver on a particular unpaved rural road at twilight on a rainy day.

Glasgow Coma Scale (DGS) – A brief clinical tool based on eye movements, and verbal and motor responses to quantify the conscious state of a person in the aftermath of a traumatic brain injury. Maximal score is 15, and a score of 3 indicates deep unconsciousness.

GPS – The Global Positioning System is a navigation system that uses orbiting satellites and provides location and time information for any person with a GPS receiver. These receivers are present in many smart phones and other personal items.

Graphesthesia – The ability to distinguish numbers or letters traced on the body, typically on the hand.

Great Recession – The worst global recession since World War II. It was marked by extreme economic decline during the late 2000s, beginning with the bursting of an $8 trillion dollar housing bubble.

Gross Motor Task or Skill – Coordination of movements of entire limbs to place the hand(s) or foot (feet) in a targeted location, or of the entire body to maintain balance or posture while standing or sitting, or for progression of the body as in walking or running.

Guardian – A person, often a family member, legally designated to make decisions for an individual lacking in capacity.

H.M. – Henry Molaison (February 26, 1926–December 2, 2008), a famous neurosurgical patient with a profound but selective memory deficit, the study of which tested theories of brain function and memory.

Hallucination – An abnormal subjective sensation or perception of something that is not actually there. It may involve any of the senses.

Hallucinations, Musical – The experience of hearing music without an actual external stimulus, often found in schizophrenia.

Hallucinations, Visual – The experience of visual perception without an actual external stimulus. These occur in primary psychiatric disorders such as mania or schizophrenia, in neurodegenerative disorders such as Lewy Body disease and Alzheimer's disease, in encephalopathy caused by drugs and metabolic disturbances, and with visual impairments as in Charles-Bonnet syndrome.

Hawthorne Effect – A situation whereby subjects behave differently than usual because they know they are being observed. The person may over- or underperform, depending on the perceived reward.

Health-Related Quality of Life (HRQOL) – A QOL domain focusing on health status, like symptoms and experiences, whether these result from physical or mental health. HRQOL measures can be generic (applicable to all individuals) or specific to a particular disease, injury, or group. In practice, measures may be labeled as QOL or HRQOL and include similar content, belying the theoretical differences between these two constructs.

Hemispheric Asymmetry Reduction in Older Adults (HAROLD) – A model of cognitive aging that postulates less asymmetric and greater bilateral hemispheric activation with aging as a compensatory mechanism for age-related cognitive changes.

Heteronormativity – The belief that people fall into one of two genders (male and female) and should naturally conform to prescriptive behaviors, roles and gender expression depending on their gender, i.e., the attitude that heterosexuality is the only normal and natural expression of sexuality.

Heteroplasmy – Mutant and wild-type mitochondria co-exist in the same cell system such as a shared circulatory system.

Hippocampus – A structure within the MTL that supports relational memory.

Hoehn and Yahr Stage – A five-stage scale using clinical markers to describe degree of progression in Parkinson's disease.

Homeostasis – From Greek homœos = similar and stasis = standing still), whereby the internal milieu is maintained close to constant in the face of external perturbations. A mechanism by which organisms function despite wide fluctuations in their environment.

Homonymous Hemianopia – Visual field deficit involving the ipsilateral vertical (right or left) half of the visual field in both eyes. It is the clinical manifestation of lesions involving the retrochiasmal visual pathways, due to colocalization of the temporal retinal fibers of the ipsilateral eye and nasal retinal fibers of the contralateral eye.

Human Factors Engineering (HFE) – HFE is a discipline and a profession that examines the interactions of humans with products, equipment, and environments during the performance of tasks and activities with the objective of improve the "fit" between the characteristics, abilities, needs, and preferences of the person with the demands associated with tasks, activities, products, and environments to maximize performance potential, safety, user satisfaction, and comfort and minimize the likelihood of errors, inefficiencies, fatigue, and injuries.

Humanities – A cluster of academic disciplines that focus on the study of human culture and artistic production, including: literature, philosophy, ethics, cultural studies, history, and creative arts (such as visual and performing arts).

Hyperkinesia – Excessive movements.

Hypokinesia – Decreased amplitude of movements.

IGF-1 – Insulin-like growth factor 1.

Impotence – A complaint, most often encountered in men and expressed as ED.

Incontinence – Inability to voluntarily control fecal or urinary excretory functions. Subtypes of urinary incontinence include urge, stress, mixed, overflow, unconscious or reflex, and functional.

Instrumental Activities of Daily Living (IADL) – Complex self-care tasks and skills needed to live independently, including managing finances, preparing meals, using the telephone, managing medications, maintaining housework, navigating public transit, and shopping.

Internalized Ageism – This occurs when victims minimize their experiences to fit with social or cultural perceptions that ageism is acceptable or justified.

Internet of Things – The idea that everyday objects connect to a network to send and receive data among personal devices, appliances, vehicles, buildings and other objects with embedded sensors, software, and actuators.

Investigational New Drug (IND) – Food and Drug Administration (FDA) designation of a drug for investigational use on approved protocols only.

Item Response Theory (IRT) – A family of probabilistic statistical tests for assessing the reliability and validity of a measure. IRT methods are also referred to as modern test theory. IRT methods focus on the individual items and the relative relationship of item responses to the probability of where the person should be placed on the underlying dimension or trait (like QOL). IRT analyses assess the "difficulty" of items along this continuum, which facilitates the use of computer-assisted testing (CAT) that minimizes the number of questions needed to locate the person's precise position on the underlying continuum.

Klotho – Membrane protein related to -glucuronidases that break down carbohydrates.

Kluver-Bucy Syndrome – A condition characterized by incontinence and sexual dysfunction. In humans, it may be associated with head injury, heat stroke, herpes encephalitis, neurodegenerative impairments, temporal lobectomy, stroke, shigellosis, psychiatric disease, and status epilepticus.

Labor Market – The supply and demand for labor, in which employees create supply and employers create demand.

Leukoaraiosis – (From the Greek: leuko=white, araiosis=rarefaction) abnormal CT and MRI appearance of the brain's white matter in the elderly, seen as bilateral patchy or diffuse areas of reduced X-ray attenuation and high T2 signal with ill-defined margins, limited to the periventricular regions or extended to the centrum semiovale.

Lewy Bodies – Intracellular inclusions of α-synuclein and ubiquitin seen in Parkinson's disease.

Long-Term Memory – Processes supporting the ability to encode, store, and retrieve information over time without constant attention.

LRRK2 – Leucine-rich repeat kinase 2, a protein that may lead to the selective degeneration of dopaminergic neurons seen in Parkinson's disease.

LTP – Long-term potentiation; two neurons that are connected have stronger connections after periods of intense activity.

Magnetic Resonance Spectroscopy (MRS) – Analytical chemical technique based on the same principles of MRI, that assesses the presence and concentration of molecular species in a sample based on their characteristic precessional frequencies in a magnetic field.

Major Depressive Disorder – A mood disorder marked by a range of depressive symptoms that must include depressed mood or lack of interest in pleasurable activities, as well as other symptoms such as insomnia, low energy, and changes in appetite.

Mania – An internal emotional state marked by elevated mood, affect and energy, often resulting in increased activities.

MAO-B – Monoamine oxidase-type B enzyme.

Medicaid– This is a joint federal and state program to help with medical costs for some people with limited income and resources, including people aged 65 and older. Medicaid may also cover services not covered by Medicare (like long-term supports and services). Each state has different rules on eligibility and applying for Medicaid. Those qualify for Medicaid in their state also qualify for extra help paying Medicare prescription drug coverage (Part D).

Medicare– The federal health insurance program for people aged 65 or older (and some younger people with disabilities and people with end-stage renal disease). Part A (Hospital Insurance) covers inpatient hospital stays, care in a skilled nursing facility, hospice care, and some home healthcare. Part B (Medical Insurance) covers certain doctor services, outpatient care, medical supplies, and preventive services. Part C (Medicare Advantage Plans) are plans through a private company that contracts with Medicare to provide Parts A and B benefits. These include Health Maintenance Organizations (HMOs), Preferred Provider Organizations (PPOs), Private Fee-for-Service Plans, Special Needs Plans, and Medicare Medical Savings Account Plans. Part D addresses coverage for prescription drugs.

Melatonin – A hormone produced by the pineal gland involved in circadian signaling of light–dark phases; levels increase in darkness typically beginning around 9 p.m. in most healthy adults.

Memory– This comprises the set of brain functions for information encoding, storage, and retrieval. These functions are essential for learning, language, remembering past events, relationships, self-identity, behavior, and action. Different types of memory are short-term memory and long-term memory. Long-term memory includes declarative (explicit) memory for storing specific personal experiences, and semantic memory, which stores factual information. Nondeclarative memory (such as implicit or procedural) refers to unconscious memories for learned skills such as bicycle riding.

Memory Disorders – These are disorders that result from damage to brain structures that underpin functions for storage, retention, and recollection of memories. Memory disorders can be progressive as in Alzheimer's disease, Parkinson's disease, and Lewy Body disease; subacute as in Creutzfeldt-Jakob disease; or acute as in traumatic brain injury, stroke or anoxia.

Metabolic Equivalents of Task (MET) – The ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. A MET also is defined as oxygen uptake in ml/kg/min with one MET equal to the oxygen cost of sitting quietly, equivalent to 3.5 ml/kg/min (Ainsworth, Haskell, & Herrmann, 2011).

Methuselah – Gene encoding for a cellular signaling protein. Mutations in this gene lead to partial elongation of lifespan in *Drosophila* (fruit fly), a model organism.

mev-1 – Gene involved in processing of reactive oxygen species. Mutations in this gene result in shortened lifespan.

Microaggressions – A term used to describe brief, everyday exchanges that send denigrating messages to certain individuals because of their group membership, originally used to describe the treatment and experiences of people of color, often falling into three categories: microinsults, microinvalidations and/or microassaults.

Microinequities – Derived from microaggressions theory, a term used to describe often unintentional, systematic discrimination through exclusion or lack of recognition.

Mild Cognitive Impairment (MCI) – MCI is an intermediate stage between the normative age-related declines in cognition and dementia. It can involve problems with memory, language, thinking and judgment that are greater than normal age-related changes and can ultimately result in dementia.

Millennials – See *Generation Y*.

Modified Rankin Scale (mRS) – The mRS is a commonly used tool to evaluate the global functional outcome of stroke. It is a disability rating scale with emphasis on walking and functional independence. The scale ranges from 0 to 6: 0, no symptoms; 1, no disability despite symptoms; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death.

Mood Disorders – Abnormal range of mood resulting in impairment of daily activities and relationships.

Movement Coordination – The motor commands that produce a spatial and temporal combination of muscle activations and joint motions to produce smooth movements of the limbs and body and to maintain balance or posture.

MRI – Magnetic resonance imaging, a method with high spatial resolution, which is designed to access cortical structure and function.

Myoclonus – involuntary twitching of muscle or group of muscles.

N1 – First negative ERP voltage deflection, with latency approximately 140 to 200 milliseconds after stimulus presentation.

N2 – Second negative ERP voltage deflection, with latency approximately 200 to 350 milliseconds after stimulus presentation.

Narcolepsy – A neurological disorder associated with excessive sleepiness or inability to maintain wakefulness, which often has accompanying hypnogogic hallucinations (typically visual in nature occurring at sleep onset), sleep paralysis, and cataplexy (loss of muscle tone provoked by sudden emotions, most often laughter).

National Eye Institute Visual Function Questionnaire (NEI-VFQ) – A survey used to assess the influence of vision on multiple dimensions of health related quality of life. There are two versions of the questionnaire, the long version with 51 questions and the short version with 25 questions. The psychometric properties of both versions have been validated through multiple clinical studies.

National Institute of Health Stroke Scale (NIHSS) – The NIHSS is a standardized way to perform neurological examination in patients with stroke. It is a quick and easy way to quantify the severity of neurological deficits in the acute setting. The total score ranges from 0 to 42. The higher the score, the more severe is the neurological deficit. It is graded mild (0–4), moderate (5–14), moderate to severe (15–24), and severe (≥25).

Naturalistic Data – Data obtained by observing a person in his or her natural environment without manipulation or intrusion by the observer. This extends ethological methods.

Neglect Syndrome – An abnormality of cognition where the individual ignores part of their own body or a portion of extrapersonal space.

Neologism – A new or novel word of an individual's own making.

Neuroculture – Describes the widespread uptake – and implied authority – of neuroscientific knowledge in lay society following the so-called "Decade of the Brain" (1990–2000), although scientific and social interest in brain function preceded this by centuries. Neuroculture is further characterized by two key assertions: (1) the brain's centrality to concepts of health and selfhood, and (2) the objectivity of modern brain imaging technologies such as fMRI.

Neuroethics – A relatively new field of ethics that focuses on issues unique or especially relevant to the field of brain science and the care of persons with dysfunctional brains, taking in to account the fact that mind and behavior are emergent properties of brain function.

Neuroplasticity – Changes in neural pathways and synapses due to changes in behavior, environment etc., as well as changes resulting from bodily injury.

Neuropsychology – A term used by Hebb in his classic book, *Organization of Behavior in Neuropsychological Theory* (Wiley, New York, 1949). Neuropsychology broadly aims to understand how brain structure and function are related to specific psychological processes, falling under broad umbrellas of thinking and emotion. Neuropsychology and related fields (e.g., behavioral neurology, clinical and health psychology, neuropsychiatry, and neurorehabilitation) use statistical techniques for standardizing psychological tests and skills to provide diagnostic and assessment tools in normal and impaired individuals.

Non-Declarative Memory – Memory of many types not included in declarative memory, including implicit and procedural memory (see *Memory*).

Non-Exercise Activity Thermogenesis (NEAT) – The energy expended for everything we do that is not sleeping, eating or exercise. It ranges from the energy expended walking to work, typing, performing yard work, undertaking agricultural tasks and fidgeting. (Levine 2002).

Non-Rapid Eye Movement (NREM) Sleep – Sleep in which rapid eye movements are typically absent. It is comprised of three stages ranging from light N1 to deep N3 sleep. N2 sleep represents the largest proportion of sleep in healthy adults, often 50 percent of total sleep time.

Nucleus Gigantocellularis – A collection of neural cell bodies located in the medullary reticular formation.

Nursing Home – A type of residential care that provides continual nursing care for individuals with frailty, injury, disability or illness.

Oculocephalic Maneuver – Movement of the head accompanying automatic eye movements in the opposite direction to keep objects in focus.

Ophthalmoparesis – Weak eye movements.

Orthopnea – Shortness of breath occurring in recumbency.

P1 – First positive ERP voltage deflection, with latency approximately 80 and 130 milliseconds after stimulus presentation.

P2 – Second positive ERP voltage deflection, with latency approximately 150 to 275 milliseconds after stimulus presentation.

P3 – Third positive ERP voltage deflection, with latency approximately 250 to 500 milliseconds after stimulus presentation.

p66shc – Protein involved in cell death. Knockout leads to elongation of lifespan in mice.

Pain Behavior – A visible or audible event (such as a limp, grimace, wince, decreased activity) that serves as an indicator of pain.

Pain Perception – The process by which pain is recognized and interpreted in the brain; it is experienced by the person, cannot be observed, and is a conscious multidimensional experience.

Pain Processing – Physiological mechanisms of pain and pain pathways, involving pain receptors, transmission of pain signals to the spinal cord, within the spinal cord, and to the brain and thalamus.

Pain Sensitivity or Threshold – The least experience of pain that a person can recognize.

Panic Attacks – Periods of provoked or unprovoked heightened anxiety lasting several minutes and usually ending within 30 minutes.

Parabiosis – Technique in which two living organisms are surgically joined to develop a shared physiological system.

Parkin – Protein implicated in early-onset Parkinson's disease.

Parkinson's Disease (PD)– A multifaceted neurodegenerative condition that affects motor function, cognition, autonomic nervous system, mood, behavior, and sleep. The "cardinal" motor manifestations of PD (parkinsonism) are bradykinesia, rest tremor, rigidity, and gait impairment.

Patient Protection and Affordable Care Act (ACA) – The ACA is a 2010 law ("Obamacare") aiming to coax hospitals and physicians to alter their practices technologically, clinically and financially for better health outcomes, care distribution and accessibility, and lower costs. Accountable Care Organizations (ACOs), Health Exchanges (state marketplaces for insurance) and Medicaid expansion (a source of healthcare funding for the elderly) are key parts of the law, which has been in dispute.

Pedunculopontine and Lateral Dorsal Tegmental Nuclei – Discrete clusters of neuronal cell bodies located in the pons and pontomesencephalic regions.

Personalized Reminder Information and Social Management System (PRISM) – PRISM was a specially designed computer system for older adults, which included a software application and a robust support system with training and instructional support. The PRISM system included a variety of features that provided easy access to resources and sources of information, opportunities for cognitive engagement, and features such as email to facilitate communication.

Personality Disorders – Maladaptive, inflexible patterns of relating to others that cause impairment in daily activities and relationships. Individuals usually lack insight about their problems.

Physical Activity (PA) – Any bodily movement produced by the skeletal muscles that increases energy expenditure; physical activity ranges from low to vigorous intensity and is positively correlated with physical fitness. Physical activity includes both exercise and non-exercise activity thermogenesis (NEAT) (Caspersen, Powell et al. 1985; Levine, 2002).

Physical Fitness – A set of attributes that people either have or achieve that are either health- or skill-related; the degree to which people have these attributes is measured with specific tests. One health-related component of physical fitness discussed in the current review is cardiorespiratory endurance, among others that include muscular endurance, muscular strength, body composition, and flexibility (Caspersen, Powell et al. 1985).

Physical Inactivity – Achieving insufficient amounts of moderate to vigorous physical activity (i.e. not meeting the specified physical activity guidelines of 150 minutes of moderate to vigorous intensity physical activity per week).

Political Economy – The intersection of economics and politics, i.e., the role of a given economic system on state policies, markets, social class, culture, populations, demographics and globalization.

Polysomnography (PSG) – A recording technique used to assess sleep, consisting of channels devoted to electroencephalography (EEG), electro-oculography (EOG), chin and limb electromyography (EMG), and oximetry, nasal airflow/pressure and respiratory effort monitors.

Population Aging – A worldwide demographic phenomenon that changes the proportion of older adults over 65 in a given population. For example, the demographics for adults over 65 are projected to change from one out of eight (2011) to one out of six (2030) to one out of four/five (2050) in the USA.

Positron Emission Tomography (PET) – A functional imaging modality utilizing short-lived, positron-emitting radiopharmaceuticals to characterize physiological processes such as cerebral blood flow, glucose metabolism, and receptor binding, as well as pathological processes such as amyloid burden in the living human brain.

Post-Concussion (Post-Concussive) Syndrome – Diagnosed when the symptomatic effects of a concussion persist for three months or longer. This complication may accompanied by abnormal cognitive and neuropsychological tests, and neural abnormalities using advanced brain imaging modalities.

Post-Traumatic Stress Disorder (PTSD) – A condition that develops in some people who have experienced single or multiple traumatic events. Persisting fear, hypervigilance, nightmares, "flashbacks," and other symptoms are outlined in *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). PTSD can be complicated by alcohol and chemical dependencies.

Preference (Utility) Models – Preference (or utility) methods and measures are used for economic-based analyses and incorporate preferences for different health states, ranging from a lower anchor of death (0.0) to an upper anchor of the best health imaginable (1.0). Weights or relative ranks are then applied to levels of health states and impairments, and summary scores are used to represent individual's (or group's) relative health and mortality experience along the continuum. This yields the information needed to determine quality-adjusted (preference-adjusted) life-years (QALYs).

Prefrontal Cortex (PFC) – Bilateral regions of the frontal lobes that are critical for cognitive function, such as attentional control and working memory.

Prevalence Rate of Dementia – The percentage of a given population with dementia (1% of 65-67; 2.1% of 75–79; 21% of 85+). In absolute numbers the WHO estimates about 47 million demented people in 2015, 75 million in 2030, and 135 million in 2050.

Proteostasis – Concepts that biological pathways that exist to control protein biogenesis, folding, trafficking, and degradation are working together to maintain functional homeostasis.

Progerin – Protein involved in Hutchinson-Gilford progeria syndrome.

Pseudobulbar Palsy – involuntary crying or uncontrollable episodes of crying and/or laughing.

Psychotic Disorders – Delusions, perceptual disturbances, or disordered thinking; sometimes diagnosed as schizophrenia or substance-induced psychosis.

Quality of Care – There are three major determinants of quality of care: structure, process, and outcome. Structure includes the available facilities, equipment, finances, staffing, and organizational structure of the healthcare establishment. Process involves what is actually being done as

healthcare is delivered to and received by the patient. Outcomes refer to the effects of care on the health status of patients and populations and includes mortality, morbidity, and QOL.

Quality of Life (QOL) – A multidimensional concept capturing self-reported, subjective evaluations about both the positive and negative aspects of life. Although health is one of the important domains, QOL includes many others like meaningful social roles, social and family relationships, social support, the social and built environments, spirituality, religiosity, autonomy, and social position. Regardless of which domains are included in QOL measures, it is often beneficial to use measures that target particular sub-groups based on age, disease, injury, or function.

Rapid Eye Movement (REM) Sleep – The stage of sleep in which REMs are seen. Healthy children and adults (but not neonates) have atonia of all skeletal muscles except for the diaphragm and extraocular muscles during this stage. REM typically comprises about 20–25% of total sleep time in healthy younger adults.

Region-of-Interest (ROI) – A selected subset of samples from an imaging data set, identified to define the anatomical boundaries of an area to be analyzed.

Relational Memory – Memory for arbitrary relations between stimuli.

REM Sleep Behavior Disorder – Lack of muscle atonia during REM sleep.

Retrocollis – Backward pulling at the neck.

Rigidity – An abnormal increase in resting muscle tone that does not vary with the velocity of movement. It is typically associated with injury to the extrapyramidal tracts of the central nervous system as can be seen in Parkinson's disease.

ROS – Reactive oxygen species, i.e., referring to a molecule's reactivity with oxygen.

S6K1 – Protein that has been shown to lead to increased longevity in mice.

Sarcopenia – A degenerative loss of muscle and strength that can occur in the elderly or frail.

Schizophrenia – A psychiatric disorder producing delusions, perceptual disturbances and/or disordered thinking, which are usually chronic and debilitating.

Sedentary Behavior – Any waking behavior characterized by a low energy expenditure ? 1.5 metabolic equivalents (METs) while in a sitting or reclining posture (Tremblay et al., 2012; Sedentary Behavior Research Network, 2013).

Short-Term Memory – Processes supporting the ability to maintain attended information across short periods of time.

Sialorrhea – Drooling.

Sildenaphil (Viagra) – Medication that treats erectile dysfunction by inhibiting phosphodiesterase type 5. Side effects include headache, nasal congestion, flushing, dyspepsia, and blue visual tint.

Sleep (REM) Latency – Sleep latency (or sleep-onset latency) is the time from "lights out" to the onset of any stage of sleep (usually N1) on polysomnography. REM latency is the time from sleep-onset to the appearance of REM.

Smart Home – A building outfitted with networked sensors and software to track occupant behavior and with actuators to control lighting, heating, appliances, and electronic devices in the home, remotely, as by phone or computer.

Social Engagement – Existence of social ties that allow individuals to take social roles and provides them with a sense of value, belonging, and attachment (Berkman and Glass, 2000).

Social Integration – Existence of relationships that allow individuals to fulfill social roles either intentionally or unintentionally (Berkman & Glass, 2000).

Social Network – Linkages between people that may or may not provide social support and that may serve functions other than providing support (Heaney & Israel, 2008).

Social Safety Net – Services provided by the state or other institutions designed to eliminate, and protect vulnerable individuals and families from falling into poverty, i.e., healthcare, food programs, financial assistance, education, social security, transportation services, etc.

Social Support – Aid and assistance exchanged through social relationships, which are intended by the sender to be helpful (Heaney & Israel, 2008).

Spasticity – An abnormal increase in resting muscle tone proportional to the velocity of movement. It is typically the result of an injury to the pyramidal motor tracts of the central nervous system.

Stimulus-Onset Asynchrony (SOA) – The temporal delay between the presentation of an initial stimulus and the subsequent stimulus.

Suprachiasmatic Nucleus (SCN) – A small collection of neuronal cell bodies located in the anterior hypothalamus, which acts as the primary controller of circadian rhythms.

Synchronization – Changes in oscillatory properties of given neural populations by either (1) increase in coherence of oscillatory neural activity within a specific frequency range, or (2) increase in proportion of units in neuronal population active in specific frequency range; quantified by relative increases in spectral power.

Tau – Microtubule-associated protein that accumulates in Alzheimer's disease.

Telomere – The sequences of DNA at the tips of chromosomes that protect the end of the chromosome and play a key role in replicative senescence. The enzyme telomerase adds telomeric sequences to the telomeres and has been associated with cellular immortality.

Testamentary Capacity – Capacity to make and alter a will.

Theory of Mind (ToM) – Cognitive abilities involved in perceiving and interpreting the mental states of other individuals, including their intentions, beliefs, and emotions.

Theta – Oscillatory neural activity observed in the 4–7 Hz spectral frequency range.

Tics – Sudden rapid jerks, usually accompanied by inner urge to perform the movement.

Title VII of the Civil Rights Act of 1964 (Title VII) – A federal law prohibiting employers from discriminating against employees on the basis of sex, race, color, national origin and religion.

Transient Ischemic Attack (TIA) – TIA refers to transient episode of acute neurological symptoms due to focal brain, spinal cord, or retinal ischemia, without infarction. The current definition is based on tissue criteria, which implies the absence of a cerebral infarction on imaging. This definition is applied independently of the duration of the symptoms.

Trismus – Lockjaw, reduced opening of the jaw because of excessive muscle contraction.

Undue Influence – The situation in which one person (or more) influences a vulnerable individual to make decisions or behave in ways different than they would if left to their own devices, and which are not in their best interests, done for the advantage of the influencer.

United States Equal Employment Opportunity Commission – See *Equal Employment Opportunity Commission*.

Useful Field of View (UFOV) – A computerized paradigm used in experimental and clinical research that consists of several subtests designed to measure attentional function.

Vascular Cognitive Impairment (VCI) – VCI refers to a spectrum of cognitive deficits, from mild to severe forms, related to cerebrovascular disease. VCI includes two broad groups, vascular dementia and vascular mild cognitive impairment. The core criteria to diagnose VCI are to (1) demonstrate presence of cognitive deficit by neuropsychological assessment and (2) demonstrate presence of vascular disease either by clinical history of stroke or by neuroimaging. Neuropsychological assessment should involve testing of at least four cognitive domains: memory, language, executive/attention, and visuospatial function. Memory deficit is not required for diagnosis of VCI.

Vestibular System – This includes the ear with the gravistatic and angular acceleration sensors, the brainstem with the vestibular nuclei including the vestibular lobe of the cerebellum (uvula, flocculus, and nodulus) and the motor output to eye muscle motoneurons, and cervical and spinal motoneurons. Also included are cortical functions of vestibular input related to place cells in the hippocampal formation that play a role in age related orientation decline.

Voxel-based morphometry (VBM) – Neuroimaging analysis technique that allows the investigation of differences in brain anatomy between groups using the statistical approach of statistical parametric mapping.

Wake After Sleep Onset (WASO) – The total time of wakefulness observed between sleep onset and final awakening on polysomnography.

Working Memory – Processes supporting the ability to manipulate (work on) attended information.

The Wiley Handbook on the Aging Mind and Brain

Part I
Introduction

1

The Aging Mind and Brain

Overview

Matthew Rizzo, Steven Anderson, and Bernd Fritzsch

Introduction

This is an opportune time for studying the aging mind and brain and translating the knowledge gained to improve the quality of life and prolong the independence of older people worldwide. Strategic national and international research efforts are gaining traction into molecules and mechanisms underpinning brain aging. Research programs leveraged by academic, government and industry partners have gained unprecedented insights into normal brain function, as a referent for detecting critical and potentially remediable cascades of dysfunction emerging much earlier in life, that may be harbingers of neurodegenerative diseases such as Alzheimer's, Parkinson's, and related disorders.

Strategic efforts to better understand brain aging need to be understood in view of demographic trends over the next few decades that favor more and longer-living seniors, and relative decline in the proportion and fertility rates of younger people. These changes have huge implications for society. Living, working, spending, and income patterns of seniors differ markedly from juniors', as do healthcare expenditures, ultimately straining government support programs and social networks to their limits. We need to address legislative issues and policies that advance discoveries and technologies and promote access and payment for needed care. We must educate ourselves on the pros and cons of new treatments by analyzing and reconciling moral issues that pit the Kantian wish to provide the greatest good for each person (for example, individualized medicine at some expense) with the Utilitarian goal of relieving disease and suffering as much as possible across the lifespan for the entire population. Personalized medicine (aka, precision, stratified, and P4 medicine) separates patients, putting individuals front and center for medical decisions, practices, or interventions based on predicted disease risk or therapeutic response[1]. How can we afford to support these needs, and how can we afford not to?

Reaping the benefits of healthy aging requires mental health for a self-directed life. The silver lining of the Grey Tsunami of aging societies worldwide is increased health of many more seniors, affording a potential "fourth phase" in their lives, inserted between ages 50 and 70 (and perhaps even up to age 100 years or more, should historic trends on increased lifespan continue). Such a phase could allow older individuals to refocus and rebalance their life plans, redefining life strategies in beneficial ways not predicted just a few years ago when expectations for productive workspan ended around age 65 years old, or a century ago, in 1920, when mean lifespan itself was merely 54 years for women and men. Increasing trends toward healthy aging offer personal opportunities to engage in productive life and promise reduced costs of age-related disease to society, assuming medical gains keep pace to preserve the health of the superannuated.

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Even with dramatically improved health in the elderly, the growing burden of increased elder care will be a defining issue of all industrialized nations over the next 50–100 years.[2] In the US, the population of centenarians will rise from 16,000 (2015) to over 1 million (2050) and to even higher numbers by 2100. The number of seniors combined with their increased longevity will strain social security and healthcare systems as senior dependents require caretaking by public and private hands. Society needs alternative strategies to engage seniors in a productive way to maintain the standard of living our society currently enjoys (in line with ongoing efforts in Japan, home perhaps of the world's oldest population). An added benefit of such engaged seniors is to maintain social and intellectual engagement for healthy mind and brain aging, and avert an older and ever-growing cohort of the impoverished, isolated, sick, bored, and despairing.

Goals of this Handbook

This handbook recognizes the critical issues surrounding mind and brain health by tackling overarching and pragmatic needs for better understanding of these multifaceted issues through a convenient source. This includes summarizing and synthesizing critical evidence, approaches and strategies from multidisciplinary research that has advanced our understanding of the neural substrates of attention, perception, memory, language, decision-making, motor behavior, social cognition, emotion, and other mental functions. Basic scientists are discovering molecular, cellular, and genetic underpinnings of neural changes that affect cognitive capabilities over the lifespan. Behavioral researchers are classifying and measuring cognitive functions in multiple domains, tracking specific changes in these over the lifespan, and uncovering factors and treatments that can maintain and improve these functions in aging brains until later in life than ever before. Explanatory models and theories of cognitive processes are being developed to interpret these changes and link them to changes in brain systems that support aging minds. Social scientists and legal experts are demonstrating the key role of cultural supports and life experiences in shaping cognitive content and processes to extremes of the lifespan. These combined advances are furthering our understanding of how aging affects cognitive functioning and informing interventions to maintain cognitive performance to the extremes of superaging.

Popular efforts continue to raise public awareness of the science and opportunities to improve aging brains[4]. To understand and improve the health of the aging mind and brain, a silo-spanning team of interdisciplinary experts in research, teaching, outreach, community engagement, public policy, and the law, has collaborated to write a book on changes in neural health and in behavioral context that occur with aging, understanding differences in cognitive function within and between individuals at baseline and over time, and advancing mind and brain health across the lifespan. The authors tackle principles and practice relevant to "evergreen" challenges posed by the US National Academy of Sciences and National Institute on Aging (NIA)[3]:

- Build the scientific basis for promoting neural health in the aging brain.
- Improve the understanding of the structure and function of the aging mind, including behavioral and neural mechanisms, and their impact on diseases and their management.
- Evaluate current methods of assessment of higher brain function and behavior and related factors across the lifespan.
- Determine how behavioral, social, cultural, and technological context affect cognitive functioning and real-world performance of aging individuals and how to intervene effectively to augment individual functioning and performance in context.
- Address legal and policy implications for promoting safety and care of persons with cognitive challenges
- Analyze practice and policy issues that impact advancing science, models of care, treatment, outreach, access to care, and quality of life.

Overview of Contents

The evidence assembled in this unique handbook is geared toward improving the recognition, diagnosis, prevention, and treatment of many brain-based disorders that occur in older adults and that cause premature disability and death. Our primary aim is to advance the care and quality of life of patients who present with perceptual, cognitive, language, memory, emotional, and many other behavioral symptoms associated with these disorders, as well as aging adults who do not meet criteria for a neurological diagnosis. Materials are presented at a scientific level that is appropriate for a wide variety of learners.

To address the critical topics and challenges in mind and brain aging we have organized this handbook into eight parts (I–VIII) comprising 36 chapters. Between part I. Introduction (containing this chapter) and part VIII. Conclusion (chapter 36), are several sections (II–VII). These are summarized below.

Part II. Theoretical, animal models, social, and humanistic perspectives

Chapter 2. Ashida and Schafer: Social networks, social relationships, and their effects on the aging mind and brain

People, like cells in a person's body, are parts of dynamic systems and a network of support. Ashida and Schafer explore how social interactions at various levels affect healthy aging, much as cells in a body depend on functions of other parts. Mechanistic details of how such social interactions affect mind and brain health remain unclear, and individual variations tend to buck trends, yet common themes of social dependency emerge. Evidence strongly supports that caregiver and care receiver form dyads driven, for better or worse, by interactive dynamics at multiple levels. Social networks and interactions benefit healthy aging, but few attempts have been made to measure these interactions and harness their potential for improving healthy mind and brain aging in a rapidly changing society—where family interactions are progressively replaced by distant social networks in cyberspace. The effects of these dynamic changes on healthy aging of an ever-increasing population of seniors ready and willing to maintain social engagement are critical areas to be explored.

Chapter 3. Prahlad and Chikka: Aging and the brain

This chapter reviews molecular and cellular aspects of aging in the context of the evolution of aging. What is the advantage to humankind of long living? Organismal aging as a postreproductive process is not under strong reproductive selection. Extensions of lifespan may even correlate with reduced reproduction. The oldest known person ever, Jeanne Calment, died at age 122 and had only one daughter. Hers is a prominent human example of a broader inverse relationship between longevity and fertility across species, whose foundations remain unclear. A central theme of aging is the molecular and cellular instability and the role of the brain in regulating these processes. Some proteins are surprisingly long lived and resist proteasome decay, leading in pathological cases to prion disorders such as Creutzfeldt-Jakob disease. The authors review how this works at molecular levels and relates to age-related cellular burden in neurons that never "rejuvenate" through cell division. Parabiosis, or sharing of blood circulation of two organisms of different age, is the best known example of how blood-born molecules can affect organism vitality and longevity, possibly through additional trophic factors in the brain. This chapter lays biological foundations for interpreting findings on the aging mind and brain covered throughout this book.

Chapter 4. Emmons, Kim, and Narayanan: Animal models of pathological aging

This detailed overview provides insights into the strengths and weaknesses offered by certain model organisms for studying the molecular basis of neuronal aging. Valuable invertebrate model organisms are described first (flies and worms), and their strengths and weaknesses for studying the effects of certain genes/proteins on longevity are provided, including the limits of transfer to

humans. Skipping nonmammalian vertebrate organisms (zebrafish, frogs, chickens), the utility of nonprimate and primate model organisms for studying age-related brain disorders is reviewed. This chapter concludes that no single model organism provides access to all the factors affecting human brain aging. Each is valuable in its own right for gaining insights not obtainable in human studies and, with proper additional testing, may prove applicable to humans.

Chapter 5. Charise and Eginton: Humanistic perspectives: Arts and the aging mind

This overview of humanistic perspectives on aging gives examples of late-life creativity, artistic portrayals of aging and the aging mind, and therapeutic applications of the arts for older persons. With reference to literature and writing, visual arts, and film, we consider how these art forms have given rise to therapeutic practices aimed at improving the lives of older people, especially those with age-related illness or disability. Given the early state of research into arts-based interventions, where possible we refer to effectiveness studies undertaken by humanities and social-science researchers and/or artist practitioners (often in collaboration with neurologists or other health professionals). This chapter argues that aging societies suffer from "Alzheimerization", preventing use of limited resources of more creative approaches toward humanity of aging. The chapter concludes with a synopsis of critical approaches to clinical neuroscience and aging, followed by new directions for advancing humanistically informed research concerning the aging mind and brain.

Part III. Methods of assessment

Chapter 6. Diesing and Rizzo: Medical assessment of the aging mind and brain

This chapter reviews essential principles, practice and approaches to assessing older persons with mental, behavioral and mobility changes. These changes are becoming more prevalent with trends toward greater longevity, aging of the general population, and associated age-related neurological disorders. Consequently, healthcare providers of all types are broadly challenged with acute and chronic impairments of mind and brain health. Primary care and cognitive and behavioral health specialists, including neurologists, geriatricians, psychiatrists and psychologists, and others, must be prepared to diagnose, treat, and refer these older patients for appropriate tests, consultation, and treatment. The related history, physical assessment, and laboratory tests in the evaluation of the aging patient are geared toward problems such as changes in mental status, emotion, pain, continence, mobility, and falls.

Chapter 7. Jones: Neuropsychological Assessment of Aging Individuals

The role and practice of neuropsychological assessment for older persons are examined. Aging is associated with decline in various aspects of cognitive function and increased risk of a number of mind-altering diseases. Neuropsychological assessment provides a safe, noninvasive method of evaluating the health of an aging brain and an objective source of information and recommendations regarding cognitive capacities. Key principles of neuropsychological assessment, training models for neuropsychologists, and evolving methods of assessment are reviewed. Neuropsychology is poised to play an ever-greater role in maintaining brain health in our aging population, including widespread screening for dementia, monitoring medication effects, and guiding cognitive rehabilitation after stroke and other age-related events.

Chapter 8. Capizzano, Moritani, Jacob, and Warren: Normal aging: Brain morphologic, chemical and physiologic changes detected with in vivo *MRI*

Brain morphologic, chemical and physiologic changes detected with *in vivo* magnetic resonance imaging (MRI) are appraised. MRI is a medical imaging technique widely used to assess structural and functional brain changes in aging. MRI scanners use strong magnetic fields and radio waves to form images of the body. The popularity of MRI methods in aging research can be attributed to its ability to probe the brain noninvasively using several different contrast mechanisms that are

sensitive to different properties of the brain tissue (e.g., water content, diffusion environment in the brain, concentration of different metabolites, perfusion, and oxygenation of blood). MRI exams involve minimal risk, and the hardware is now widely available, which makes it an ideal tool in aging research and clinical practice. This review focuses on the changes detected in the brains of healthy elderly subjects as detected by means of state-of-the-art MRI techniques used to assess brain structure and volume (structural MRI), water diffusion (diffusion weighted MRI: DWI), biochemical composition of tissues (MR spectroscopy, MRS), neuronal activity (functional MRI: fMRI) and cerebral perfusion (perfusion MRI). Nuclear medicine functional neuroimaging studies and findings in different types of dementia patients will be reviewed in the corresponding chapters of this book. This chapter complements chapter 9 on positron emission tomography (PET) and chapter 10 on electrophysiologic techniques.

Chapter 9. Boles Ponto: Positron emission tomography (PET) imaging: Principles and potential role in understanding brain function

This chapter provides an overview on PET in terms of strengths and limitations as well as specific use in certain brain pathologies. A limitation of PET is that the use of fast-decaying nucleotides requires proximity to sources of such nucleotides typically justifiable only with a large enough patient basis. Despite these practical limitations, research and clinical roles of PET imaging are well-established, especially for the evaluation of blood flow and glucose metabolism in a variety of neurological and psychiatric conditions. The role of amyloid imaging in the evaluation of an individual's risk for the development of Alzheimer's disease is beginning to be clarified and may become a critical part of the selection of subjects for Alzheimer's disease treatment trials. PET has also proven to be effective in seizure diagnosis. The broad range of potential PET radiotracers and the extensive neurotargets yet to be explored indicate the crucial role that PET can play in our quest to understand the human brain, both its normal function as well as its disease state and during aging.

Chapter 10. Anderson and Taraschenko: Electrophysiological measures of age-related cognitive impairment in humans

Anderson and Taraschenko review current experimental and clinical applications of electroencephalography (EEG) for the assessment of age-related cognitive impairment. EEG records near-instantaneous voltage fluctuations generated by large populations of postsynaptic potentials, providing a measure of neural activity with the high temporal resolution required to study rapid cognitive processes impaired in the aging brain. Quantitative analysis of EEG has revealed age-related changes in properties of oscillatory neural activity across multiple spatiotemporal networks. Event-related averaging methods have demonstrated changes in stimulus-evoked potentials across cognitive modalities in the aging brain. Likewise, longer latency-evoked potentials reflecting neural activity generated by downstream cognitive processes have been shown to be altered in older adults. Studies reviewed here are discussed in the context of existent behavioral and structural imaging data and discussed within a theoretical framework provided by putative compensatory models of cognitive aging. Finally, limitations of current EEG research are discussed, and future directions for the field are described.

Chapter 11. Rizzo and Rizzo: The brain in the wild: Tracking human behavior in naturalistic settings

Measuring brain activity is critical to understanding the mechanisms and controls of behavior and require tracking "the brain in the wild." Researchers have been tracking activity in the brain for several centuries, in model organisms and in human test subjects, and many of these investigations have depended on the control afforded by a laboratory setting. While laboratory research can provide unparalleled opportunities to explore the brain in isolation, researching in these controlled settings can also create drawbacks in the pursuit of an accurate understanding of the who, what, when, where and why of brain activity in naturalistic (real-world) settings. Human behavior observed in laboratory settings may differ markedly from that exhibited in nature ("the wild"). Test subjects may be

frustrated by the task at hand and underperform on clinical testing as a result. Conversely, test subjects may be acutely aware measurement is taking place and may overperform on clinical tests. One solution to this problem is to use self-reporting or interviews to glean insights on what activity actually occurs in naturalistic settings. However, memory isn't a foolproof record of reality, and biases or lack of training on the part of the observer or subject can create filtered reporting that results in a lack of actionable data. Even when self-reporting is accurately able to capture behavior in field conditions, proxy measurements produce additional complications. Whether the data being examined is an accurate determinant of a behavior or outcome is a difficult question. If an individual scores well on an IQ test, this does not guarantee he or she will succeed in terms of choices and activities at home, work, or play. To address these considerations of validity, we need metrics of the "ground truth" of everyday life. Rizzo and Rizzo explain how they examined older life gains from emerging technology in terms of healthy brain aging, independence, and quality of life.

Chapter 12. Wolinsky and Andresen: Quality of life assessment

This chapter traces the intellectual origin of the concept of *quality of life* (QOL), offers the World Health Organization (WHO) conceptualization of QOL and criteria for its measurement, and a perspective of QOL and health-related QOL (HRQOL) discussions. Standards for QOL methods and measurement advocated by several groups are presented in the second section as well as special considerations for older adults like cognitive impairment and dementia, the end of life, and the use of proxy-respondents. The third section of the chapter focuses on the two main families of generic QOL and HRQOL measures, those of the WHO and the Medical Outcomes Trust and QualityMetrics partnership. In the fourth section one preference (utility) measure for each of these two families of generic QOL and HRQOL measures is outlined. In the final section three QOL measures specifically constructed for the special circumstances of older adults are presented.

Part IV. Brain functions and behavior across the lifespan

Chapter 13. Eslinger and Flaherty: Executive functions and behavior across the lifespan

Executive functions (EF) are here defined in conceptual and practical behavioral terms. A framework is developed that broadly describes the maturational trajectory of EF across the lifespan and how EF relate to the primary cognitive constructs of intelligence, language, spatial perception, and memory. Most importantly, the linkage between EF and continuing adaptation in adulthood and especially aging is emphasized. The "frontal executive" theory of aging is presented and related to the broader cognitive aging and cognitive reserve literature. In this way, specific aspects of working memory, decision-making, and social cognition can be highlighted. Distinctions between executive aging and executive dementias are addressed with pragmatic assessment and management recommendations.

Chapter 14. Warren, Rubin, Shune, and Duff: Memory and language in aging: How their shared cognitive processes, neural correlates, and supporting mechanisms change with age

This chapter provides an overview and discussion of two quintessential human abilities that change over the course of our lives: memory and language. The chapter begins with a summary of cognitive aging findings focused on memory abilities, and following that section is a similar summary of cognitive aging findings addressing language abilities. Several relevant theories of cognitive aging that are applicable to the study of memory, language, or both are then considered. The chapter concludes with a discussion of the promise of research probing the intersections of memory and language through behavior, neuropsychology, and neuroimaging, which point towards possible shared mechanisms.

Chapter 15. Owsley, Ghate, and Kedar: Vision and aging

Vision impairment is among the top 10 causes of disability in the United States and is particularly prevalent among older Americans due to common problems such as presbyopia, cataract,

glaucoma, macular degeneration, and, less commonly, brain disorders such as stroke, tumor, and neurodegenerative disease. A million Americans are blind and millions more have low vision—irreversible vision impairment (best-corrected visual acuity worse than 20/40 or field loss of less than 10 degrees from fixation). Vision impairment not only causes difficulties with the visual activities of daily living such as reading and mobility, but also has been associated with a number of adverse outcomes including depression, loss of personal independence, social isolation, transportation challenges, unemployment, placement into long-term care, and death.

Chapter 16. Fattal, Hansen, and Fritzsch: Aging-related balance impairment and hearing loss

An overview of the structure, function, pathology and countermeasures of the motor system related to balance, as well as the major input via the vestibular system and the closely associated auditory system is provided. The motor control system of human bipedal walking and its levels of spinal, brainstem, and cortical control as well as loss of control in different pathological states is first described. This is followed by the detailed analysis of the vestibular system, including how that system ties into the motor control of balance and loss thereof, leading to falling in the elderly. The auditory system is included here, as it is closely related to the vestibular system of the ear and shows similar but more accelerated age-related decline. The auditory system is unique among all sensory systems, as an electronic prosthesis, the cochlear implant, can restore some hearing in deaf patients. Similar vestibular implants are in advanced stages, making the ear unique among all senses in terms of electronic substitution.

Chapter 17. Lester, Vatterott, and Vecera: Attention and processing speed

Aging and degeneration of the brain can result in forgetfulness and difficulties interacting with complicated or novel environments, including instrumental activities of daily living. Many aspects of these difficulties are rooted in impairments of speed of processing and attention. The chapter by Lester and colleagues examines the interaction of aging and selective attention, which depends on the integrity of cortical and subcortical structures, including the reticular activating system of the brainstem. Modern concepts of aging and attention have expanded considerably beyond a processing speed account into models of distributed functional connectivity in the brain. The chapter concludes with interventional approaches to cognitive aging and attention decline through various "neuroenhancement" techniques.

Chapter 18. Darling, Cole, and Ashton-Miller: Motor functions and mobility

This chapter provides an overview of the effects of aging on motor function and mobility in healthy individuals, focusing on gross and fine movements of the upper limb, whole body posture, and locomotion. The chapter details the motor changes associated with aging, pointing out the progressive slowing of movement with increasing age. Subsequently, the chapter highlights many of the attempts made to mechanistically understand the age-related slowing and their neurosensory control mechanisms. Both cortical and subcortical motor control areas show age-related alterations that could play a role in the slowing of movement, but little evidence exists to pinpoint exactly how each of these various motor control pathways relates to the slowing of movements.

Chapter 19. Kreder, Faris, Rao, and Rizzo: Incontinence and sexual dysfunction

The diagnosis and treatment of incontinence and sexual dysfunction, conditions that are particularly prevalent among the elderly, are discussed. These troublesome and costly healthcare problems can be caused by lesions at several levels of the nervous system in association with lesions in the peripheral nerve, spinal cord, and brain. Some patients have neural lesions at more than one level, as in diabetes, alcohol abuse, and multiple sclerosis. Vascular pathology, medication effects, and psychiatric factors further complicate the assessment and treatment of these patients. Incontinence is a significant threat to independent living and an important factor in nursing home placement. Neural substrates and treatments of these complex biological and psychosocial phenomena are active areas of multidisciplinary research and keen public interest.

Chapter 20. Chen and Anderson: Aging and emotional functioning

Changes in emotional function associated with aging are reviewed, including profiles of change, factors that appear to shape these profiles, and implications for successful aging. Emotional function in older age is strongly associated with quality of life, physical health, and mortality risk but remains poorly understood. This chapter first describes age-related changes in discrete negative emotions (anger, sadness, fear, and disgust), positive emotions, social cognitive and self-conscious emotions, and in the intensity and complexity of emotions. Then, factors are reviewed that may mediate/modulate changing emotional status in older age, including sex differences, culture, personality, and the social/work environment. The third part of the chapter reviews contemporary theories and models of aging and emotion. Finally, a new integrated perspective on aging and emotion is presented, which brings together a number of features from existing theories and models, with an emphasis on the compensatory interactions between age-related strengths and weaknesses. The model incorporates age-related differences between various types of discrete emotions, different levels of emotional challenge, stages of emotion generation and regulation, and phases of the dynamic process of emotion.

Part V. Brain disease and dysfunction

Chapter 21. Jones, Bruns, and Petersen: Alzheimer's disease and mild cognitive impairment

Dementia is a primary concern for many elderly individuals, and among the dementias, Alzheimer's disease (AD) is by far the most common cause. While AD is not an inevitable consequence of aging, its frequency increases dramatically among people over the age of 70. There were approximately 4.5 million people with AD in the United States in 2000, and this number may increase to 14 million by 2050. Greater attention is merited on possible precursors to AD, such as mild cognitive impairment (MCI). Growing evidence supports gradual progression of the pathologic process from normal aging to MCI to clinically probable AD. Individuals experiencing this progression must be identified and monitored through a variety of means including neurological examination (see chapter 6), imaging (see chapter 8 and chapter 9) and other biomarkers, and through new technologies and approaches for real world monitoring (see chapter 11). Jones et al. review these issues and relevant evidence, opinions, and practice parameters from the American Academy of Neurology concerning MCI, diagnostic issues concerning AD and other dementias, and related treatment recommendations from the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroups on diagnostic guidelines.

Chapter 22. Nagaraja and Leira: Cerebrovascular disease and white matter disorders.

About a third of blood pumped by the heart with every contraction circulates through the brain, which critically depends on this steady supply for normal neuronal function. Nagaraja and Leira detail in their chapter the multiple facets of vascular-related brain dysfunction, ranging from stroke to white matter atrophy due to limited blood circulation. As expected, strong correlations of vascular diseases of the brain exist with age, weight, and diabetes. Arguably, vascular diseases are likely the largest single cause of dementia and certainly play a major role in Alzheimer's disease. Countermeasures in terms of various treatments after stroke or to prevent vascular diseases are discussed and put in the context of well-known preventive measures such as exercise, reduced blood pressure, and low levels of cholesterol related to appropriate dietary intake such as the Mediterranean diet.

Chapter 23. Lamichhane and Uc: Movement disorders

This review of motor disorders categorizes such disorders into those with excessive, abnormal, decreased, slow, and loss of movement. For each of these categories, overviews are provided of the clinically relevant disorders and how these disorders relate to aging (most show a strong age dependency in frequency of occurrence). This chapter provides a detailed account of diagnostic features of various movement disorders (e.g., Parkinson's, Huntington's), and points out similarities

and dissimilarities between disorders that fall overall into the same categories. The preferred therapeutic intervention is provided for each movement disorder and put into the perspective of side effects. The authors also present side effects caused by certain treatments of a given disorder that mimic other disorders, thus clearly relating the complexity of intervention with currently available treatments.

Chapter 24. Wengel, Cervantes, and Burke: Psychiatric disorders

Many psychiatric disorders found in younger adults extend into the senior years. Beyond this obvious discernment, Wengel et al. present in their chapter a more detailed insight into late-appearing psychiatric disorders and their relevance as warning signs of underlying brain dysfunction. Such late-onset psychiatric disorders may be the result of early life experiences, may be related to neurologic disorders as compromising additional effects or may manifest themselves as side effects of pharmacological treatments of seemingly unrelated disorders. In many of these late-onset disorders it is essential to understand the patient's life history to evaluate the likely causes and conclude with proper treatment. While certain treatment may result in easy relief of the symptoms, other cases, in particular of personality disorders, require long-term care to reduce the symptoms, with no cure yet in sight. Both family and professional caregivers need to be properly informed about those diseases to endure the stress associated with caring for such elderly patients.

Chapter 25. Serrano-Pozo: Encephalopathy

This chapter on encephalopathy (Greek, from *enkephalos* – brain and *pathos* – disease) includes coverage of clinical manifestations, etiologic classification, specific subtypes, and diagnostic work-up. Encephalopathy implies an anatomical correlate in the brain and a functional correlate in terms of brain dysfunction or failure. *Altered mental status* and *delirium* fall under the larger umbrella of encephalopathy and describe functional manifestations. Encephalopathies can be classified as acute (hours to days), subacute (weeks to months) or chronic (>6 months) as in Alzheimer's disease. Serrano-Pozo focuses on the acute and subacute encephalopathies that require prompt inpatient diagnostic work-up and pose immediate challenges to clinicians. Chronic encephalopathies, addressed in other chapters, are mostly irreversible dementing processes typically seen in the outpatient setting, including Alzheimer's disease and related disorders (see chapter 21), vascular disease (see chapter 22), chronic traumatic encephalopathy (see chapter 26), Parkinson's disease (see chapter 23), and other disorders.

Chapter 26. McGuire: Traumatic brain injury and neurodegenerative disease

Moderate or severe traumatic brain injury (TBI) has been linked to an increased risk of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. In contrast, mild TBI (or "concussion") has only recently been considered a risk factor for progressive neurodegenerative disease, except for "punch drunk" syndrome, or *dementia pugilistica* which was presumed to be confined largely to professional boxers. In 2002, Bennet Omalu, a forensic pathologist, identified changes of dementia pugilistica in the brain of a retired National Football League (NFL) player, and subsequent autopsy series found this pathological fingerprint in veterans of ice hockey, wrestling, soccer, and other contact sports players with histories of concussions. Chronic traumatic encephalopathy (CTE), now the preferred term, has been confirmed in football players with no reported concussions, but with predictable exposures to head trauma in practice and play, and in military veterans with histories of blast-related or other mild TBI sustained in combat. McGuire underscores that cognitive, motor, and neuropsychiatric manifestations have emerged years after mild TBI, usually repetitive, in confirmed cases of CTE. Decline in memory, poor judgment, executive function impairment or frank dementia may be preceded or accompanied by neuropsychiatric symptoms such as depression, increased aggression, and suicidality. Gait abnormalities, Parkinsonism, weakness, and dysarthria are well-described features in some affected individuals. Hence this clinically heterogeneous spectrum may imitate several dementing illnesses in older individuals. Common comorbidities such as vascular disease, diabetes, and alcohol and substance abuse,

undoubtedly influence presentation and progression. As yet, CTE remains a postmortem diagnosis with unknown incidence and prevalence, and there are no consensus-based or prospective, validated clinical diagnostic criteria. Increased public awareness has led to legislation in all 50 states on detection and evaluation of concussion in school sports along with partnership among the National Institutes of Health (NIH) NFL, and Foundation for the NIH.

Chapter 27. Tippin: Sleep and sleep disorders in older adults

Complaints of poor sleep and daytime sleepiness are common in older adults. Frequent nocturnal awakenings, early morning awakening, excessive daytime sleepiness, and daytime napping are often encountered. Many older adults have a phase advance in their circadian rhythm leading to a tendency to go to sleep and awaken earlier than usual. Some of these changes may be the consequence of aging-related changes in the brain, but often they are the result of potentially reversible medical and psychiatric illnesses. Neurodegenerative disorders such as Alzheimer's and Parkinson's diseases may exaggerate these issues. In addition, there are sleep disorders that are either specific to this age group or become more prevalent with aging, such as restless leg syndrome, obstructive sleep apnea, and rapid eye movement sleep behavior disorder. Attention to potentially reversible comorbidities and conditions commonly seen in the elderly is crucial for proper management of sleep-related problems in older adults.

Chapter 28. Herr, Gibson, and Hadjistavropoulos: Pain

This chapter reviews key points on the experience of pain, strategies for identifying and assessing pain, and approaches to treatment in persons with dementia. Over the past decade considerable advances have been made in knowledge and approaches to addressing the many challenges faced by clinicians caring for persons with dementia and pain. However, the evidence to guide practice is still limited, leaving clinicians to make judgments by extrapolating information from studies on adults and/or older adults without cognitive impairment. As the population of persons with dementia rapidly grows over the next 30 years, targeted research that includes sufficient representation of this vulnerable group to judge treatment effects is essential to provide a rational basis for their treatment. Specifically, understanding the mechanisms and etiologies of pain in various forms of dementia, discriminating pain better by unifying language describing pain, standardizing observation tools, and implementing long-term cost-effective care are needed to manage pain.

Part VI. Optimizing brain function in health and disease

Chapter 29. Voss: The benefits of physical activity on brain structure and function in healthy aging and age-related neurological disease

Voss presents an overview of the positive effects of physical exercise on brain function, including some potential molecular explanations for the exercise effect. Interestingly, the data derived from human and mammalian animal models clearly demonstrate consistency of this correlation even in cases of neurological disorders. The century old statement "Mens sana in corpore sano" (a healthy mind in a healthy body) is bestowed with new meaning through these thorough and controlled studies. Importantly, most evidence points to mild exercise as being sufficient to generate the benefit of added neuronal plasticity. The absolute quantification of how physical exercise correlates with long-term mental benefit remains to be elucidated. Importantly, given the overall similarities in mouse and human on this benefit, it seems to be possible to use the power of the mouse model to unravel the molecular pathways leading to this benefit.

Chapter 30. Czaja: Aging, mind and brain: A human factors engineering perspective

This chapter addresses the key role of human factors engineering (HFE) for addressing growing challenges and opportunities associated with population aging, with a focus on an older user-

centered design approach. This includes examples in the realms of task and equipment/product design, training and instructional design and a précis on assessment and evaluation, and discussion of needed research in this area. HFE can greatly enhance the development of strategies to address normative age-related and disease-related changes in cognitive abilities and function experience. HFE examines the interactions of humans with products, equipment and environments during the performance of tasks and activities. This improves the "fit" between the characteristics, abilities, needs and preferences of the person with the demands associated with tasks, activities, products and environments to maximize performance potential, safety, user satisfaction and comfort and minimize the likelihood of errors, inefficiencies, fatigue and injuries. This might include ensuring that the labels on medication bottles are legible to an "aging eye" (see chapter 15) or providing environmental support aids to reduce demands on working memory or provide adequate training and instructional support. It might include designing electronic health record interfaces that consider visual capabilities and training needed to accommodate older healthcare workers (for an ethical and legal perspective see chapter 35).

Chapter 31. Williams and Jao: Community and long-term care supports for older adults with cognitive decline

This chapter reviews the current status of senior care with a projection of future needs based on demographic trends. Meeting self-care and family caretaker needs in progressive dementia can be financially and emotionally draining. Family caregiving ability is often undermined by changes in family structure and the progressive needs of demented family members. Professional care, resources and facilities are needed to accommodate these problems, with a range of costs and benefits. The chapter emphasizes the importance of assisted living facilities for early stages of professional caregiving needs in transitions to more intense and costlier hospice care. Successful care plans depend on knowledge of individual patient and family characteristics and proper diagnosis and staging of disease. With the aging baby boomer cohort, a comprehensive strategy is needed to support burgeoning annual dementia costs, which are expected to exceed $1 trillion by 2050.

Part VII. Legal and ethical issues

Chapter 32. Anderson: Neuroethics of aging

This review discusses a number of neuroethical issues raised by the rapid scientific advances in our understanding of the aging human brain, and by the care of individuals with aging minds. Many of these issues stem from the fact that aging often is accompanied by suboptimal neurocognitive function, which can appear in a dynamic fashion with an infinite number of variations in time course, severity of deficits, and profile of change. The implications of this for personal autonomy, sense of self, and self-determination cut across medical care, public health and safety, and the conduct of aging research involving human subjects (see chapter 34 on competency and capacity, and chapter 33 on public policy). Additional ethical questions have arisen because the ability to predict age-related neurologic disease has outstripped the ability to treat these conditions—an imbalance which is not likely to change in the near future. Continued scientific advances in the neuroscience of aging must be accompanied by ongoing consideration of the thorny ethical issues involved. Aging with autonomy and dignity is a universal goal that arouses considerable general interest and provides fertile ground for public engagement, education, and discussion of the neuroethics of aging.

Chapter 33. Kaskie and Stamy: The public health challenge presented by the growing population of persons with Alzheimer's disease and other forms of dementia: A survey of American public policy activity

This overview of activities to counteract the demographics of dementia, estimated by the World Health Organization (2014) to be about 35 million people worldwide, presents policy approaches to the most common chronic and disabling conditions among the elderly. Dementia became

defined as a national public health problem in the late 1970s, being among the most costly Medicare beneficiaries. The federal administration has steadily expanded efforts to address the challenges presented by dementia through Medicare, Medicaid, and the Older Americans Act. By 2014, every state had enacted at least one policy that identifies persons with dementia as a protected class and/or supports dementia-specific programs and services, but no single type of law has been enacted by every state and no single state has enacted every type of law. Despite considerable progress, much remains to be done to advance dementia policy at both federal and state levels. Through the assembly of task forces, the development of strategic plans, the identification of legislative champions, the support of bureaucratic agencies, and the empowerment of private enterprise and advocacy organizations, dementia policy will be moved forward to counterbalance the demographic predictions of the "silver tsunami" of elderly.

Chapter 34. Barrash: Competency and capacity in the aging adult

This chapter focuses on the myriad factors involved in determining an elderly individual's capacity for decision-making and other complex activities. The historical and legal roots of competency determination, and the distinction between competency and capacity are reviewed. The specific cognitive and functional capacities required to meet legal standards for various forms of capacity, and the wide range of specific neuropsychological capabilities underpinning them, are also reviewed. The clinical evaluation of capacity for specific activities is outlined, with particular attention to factors affecting cognitive and functional abilities in the elderly (medical/neurological status, emotional and psychiatric status, medications, environment, social support—each of which may impart positive or negative influence), as well as other factors relevant to capacity (e.g., personal values and cultural influences). Emphasis is placed on conceptualizing capacities not in a dichotomous "present/absent" fashion, but instead tailoring nuanced impressions and recommendations to the specific individual. The factors promoting and compromising capacity identified from the evaluation should contribute to a judgment that is minimally restrictive, balancing the patient's rights and independence with protection of the patient and society. The evaluation also should provide a blueprint for the individual, family and other care providers, and professionals to implement approaches to remediation and accommodation that optimize the individual's capacity and level of functioning.

Chapter 35. Reavis and Park: Boomers after the bust: Ageism and employment discrimination after the Great Recession

This overview of the national context of labor force participation and employment provides trends after the Great Recession and associated societal challenges. This chapter explores the significance of the continual growth of the "55-plus" workforce as well as the impact of gender in employment, particularly for older workers. It demonstrates the impact of ageism and age discrimination throughout to the employment cycle of older workers, offering a review of relevant federal and state laws and procedural avenues and their limitations, and concludes with recommendations on protecting and incorporating older workers in the labor market. The chapter can be read in the context of the many physical and health challenges reviewed in other chapters including measures for better design of tools to support work-related tasks (as in chapter 30) and Kaskie and Stamy's review of public health challenges presented by the growing population of persons with functional and cognitive decline (chapter 33).

Key points, key readings, and Glossary

Each chapter includes key points and key readings to make this handbook more transparent and accessible to readers. Increasing precision of terminology and agreement on meanings is an essential dimension of advancing the recognition, diagnosis, treatment and research of mind and brain health and the Glossary section at the beginning of this book is meant to identify and clarify this common vocabulary with working definitions. These terms have grown in number and importance in step with the blossoming of behavioral neurology, neuropsychology, neuropsychiatry, and connections to

technology and the social sciences. Related growth of public discourse, awareness, interest, and understanding is also attributable to healthcare policy and initiatives. These include the Decade of the Brain initiative, Alzheimer's Disease Initiative, Human Connectome Project, Patient Protection and Affordable Care Act, 21st Century Cures Act, along with burgeoning public exposure and fascination with research findings amplified through modern news and social media, and a general desire to understand and cure disorders of brain and behavior across the lifespan.

Audiences

We are not aware of any single current source such as this handbook that so broadly addresses the needs of potential audiences interested in the aging mind and brain. Topics span psychology (cognitive science, social science), cognitive neuroscience, physiology, biology (genetics, molecular biology), neuroimaging, computer science, human factors/ergonomics and human systems integration, medicine, nursing, social work, ethics, law, humanities, and public policy.

Potential audiences span academia, industry, and government. This includes researchers and practitioners wanting to undertake studies of aging and cognition, state and federal program managers wanting to fund relevant research, and public health officials charged with decisions on funding research projects at the state and national levels. Potential readers also include pharma industry researchers testing drugs to mitigate cognitive aging and dementia, scientists and engineers developing sensors to measure physiology and behavior (at home, work, and hospitals and in cars across the "internet of things" and in "the wild"), and faculty teaching graduate programs who want to supplement the material on mind and brain aging available to their students.

The healthcare audience includes professionals who are often called upon to advise patients with a wide range of age-related impairments. These include physician assistants, nurse practitioners, occupational therapists, pharmacists, physical therapists, social workers, and doctors, such as neurologists, psychiatrists, internists, family practitioners, psychologists, and geriatricians who care for patients in routine and specialty practices, as well as their students, who include interns, residents, fellows, postdoctoral scholars and others students at all levels, for whom interdisciplinary curricula are being developed, more and more, around the world. We understand that the audience can also include curious laypersons, patients, families, and community members interested in advancing mind and brain health for older citizens in their own communities.

We hope this handbook is useful to you. To quote the as-yet-to-be-born Star Fleet Officer Spock and his departed earthly vessel, Leonard Nimoy, "Live long and prosper," or, if you prefer the biblical, "Long life to you! Good health to you and your household! And good health to all that is yours"! (1 Samuel 25:6).

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Part II

Theoretical, Animal Models, Social, and Humanistic Perspectives

2

Social Networks, Social Relationships, and Their Effects on the Aging Mind and Brain

Sato Ashida and Ellen J. Schafer

Key Points

- Increasing evidence shows the behavioral, perceptual, and biological pathways by which social relationships and social networks positively impact health outcomes, including those for the aging mind and brain
- The facilitation of healthy aging, in turn, has been shown to increase social participation among older adults through community-based interventions and contributes to societal well-being.

"Healthy Aging" as Physical, Mental, and Social Well-Being

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] This definition emphasizes the importance of quality of life and social well-being and highlights the need to consider the impact of the social environment on human health. Public health interventions that target both the individual and his or her social environment embrace a holistic, ecological perspective that is very important for healthy aging. The ecological model posits that changes in the social environment will produce changes in the individual by addressing not only individual factors, but also interpersonal, organizational, community, and policy factors that support individual behaviors.[2] With respect to aging, active engagement in social settings, or the social environment, is an important factor leading to productive and "successful aging."[3] Although the process of aging is inevitable, epidemiological studies clearly show that the diseases and disabilities often associated with aging are not. Many of these "aspects of usual aging can be avoided or reversed"[4,5] which suggests "chronological age per se is a relatively weak explanatory variable in assessing the prospects of continuing to age well in later life."[6] Social relationships affect human immune function,[7–9] brain activity,[10] and stress response.[11] Therefore, attempts have been made to enhance social integration among older adults,[12] exemplified by the inclusion of "active ageing" as a WHO goal for policy and program formulation.[13] The WHO defines "active ageing" as "participation in social, economic, cultural, spiritual and civic affairs, not just the ability to be physically active or participate in the labour force."[13] By enabling older adults to remain productive and fully engaged, our society will continue to benefit from the resources this rapidly growing segment of the population provides.

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The impact of the social environment and relationships on individual well-being is greater in older age versus younger.[14,15] Support provided by family and friends becomes increasingly important especially when age-related diseases and disability occur. Nevertheless, age-related physical and functional decline can limit individuals' ability to maintain social relationships. Thus, it is important that we understand social network and relationship factors that influence, and are influenced by, the well-being of older adults. Such an understanding can enhance the development of interventions to prevent or delay the onset of major chronic conditions and to better support those experiencing physical and cognitive difficulties. As the number of older adults with moderate to severe disability continues to increase,[16] consideration of social support networks and relationships becomes vital to facilitating healthy aging. In this chapter we introduce the concepts of social networks and social relationships, review the literature on their relationships to health, and present current research and programs addressing social factors and cognitive health. In addition, we discuss the implications of aging-related illness, specifically dementia, on familial social network systems and conclude with a discussion of implications for research and practice.

Toward Defining Key Terms and Concepts: Social Networks and Social Relationships

Studies investigating social relationships have evolved in many different disciplines. In the field of public health, terms such as 'social integration,' 'social networks,' 'social support,' and 'social engagement" have been introduced in studies investigating the associations between social factors and human health. *Social integration* has been defined as the existence of relationships which allow individuals to fulfill social roles either intentionally or unintentionally.[17,18] This concept has been used to investigate individuals' social connectedness within society, and an impressive array of evidence indicating an association between social integration and health has been amassed. However, social integration has also been identified as one of the least understood constructs of social relationships[17] as different studies have evaluated social integration in various ways. The *social network* has been defined as "linkages between people."[19] and provides context for the exchange of social resources (e.g., support, information) and connections. Social networks can be examined by looking at their *compositional* and *functional* characteristics.

The *compositional* characteristics of social networks include network size, density, and homogeneity of the network members, and are expressed in terms of the network system as a whole. Some of the interactional, or dyadic, characteristics which concern the relationships between network members, including reciprocity of social exchange, frequency of contact with network ties, intensity of emotional closeness, and durability of relationships in terms of network stability,[17,19] also give rise to the network composition. Five key *functional* characteristics of social networks have been identified in the field: social support, social engagement or companionship, social influence, social undermining, and social capital.[17,19] Of those, social support and social engagement are most pertinent to topics of the aging mind and brain. *Social support* is defined as "aid and assistance exchanged through social relationships" that is intended by the sender to be helpful[19] and further categorized into four main types: emotional ("expression of empathy, love, trust, and caring"), instrumental ("tangible aid and services"), informational ("advice, suggestions, and information"), and appraisal support ("information that is useful for self-evaluation").[19,20] Some social relationships may not involve the exchange of social support, but exist for a "purely pleasurable interaction"[21] that facilitates *social engagement*. The existence of these ties allows individuals to take social roles and provides them with "a sense of value, belonging, and attachment".[17]

The impact of social support on health and well-being has been studied to a much greater extent than the impact of social network characteristics viewed more broadly.[17] In a convoy model introduced by Antonucci, personal and situational characteristics are thought to influence social

network structures and functions as well as network adequacy, and all of these factors impact individuals' well-being.[22] For example, social networks are influenced by larger social contexts such as the community and neighborhood and norms of reciprocity or social trust that exist within them, sometimes referred to as *social capital*. The way social networks influence individuals can be partly determined by community resources and the network's ability to access these resources and contacts.[23] Evidence suggests that strong personal social networks consisting of family and neighbors can help reduce negative impacts of urban segregation among individuals living in poverty.[24] Cohen and Wills[25] reviewed two ways social relationships influence health: "stress-buffering" where social networks are thought to provide interpersonal resources to cope when individuals face stressful events, and "main effects" where social networks provide a context in which individuals can be socially engaged, or the degree of one's integration in a large social network.[25] Evidence suggests that these two pathways are likely to coexist.[26] In the context of the aging mind and brain, it is beneficial to consider these various types of network characteristics when investigating their associations with health in order to inform future research and practice.

Relationships between Social Networks and Health

Social relationships influence individuals' perceptions of social meanings, values, beliefs, attitudes, and actions. Changes in social relationships can create positive or negative emotional states, which may lead to changes in psychological states and symptoms of mental and physical well-being.[26] During the past 40 years, this topic's popularity among health professionals has been reflected in an increasing number of review articles.

All-cause mortality

Cassel introduced one of the earliest reviews of the literature on this topic, and pointed out that social relationships might impact a wide range of factors influencing well-being through improvement of generalized resistance to health-detrimental factors rather than to specific diseases.[27] More recently, Seeman and Crimmins also stated that evidence exists highlighting the roles of social relationships on general health.[28] Numerous longitudinal epidemiological studies found that social integration and social network characteristics have predictive power in relation to "all-cause mortality" after controlling for demographics and baseline health status.[29–36] For example, in one prospective study, a 13-year mortality gradient across different social participation levels among adults ages 65 and older living in the community setting was documented.[37] Studies have also shown the protective effects of social engagement and support in the context of cardiovascular disease, with evidence supporting lower mortality due to cardiovascular disease among those who are socially engaged.[38–42] Similarly, in a cohort of patients with first cases of ischemic stroke, social isolation was shown to predict a first occurrence of myocardial infarction, stroke recurrence, or death[43] and the mortality rate was shown to be higher among socially isolated individuals with significant coronary artery disease.[44]

Physical and psychological well-being

Although the association between social network factors and mortality has been documented fairly consistently, their association with morbidity is less consistent.[45–47] In one study, visiting friends and participating in groups for older adults was positively associated with physical functioning and general well-being.[48] A strong positive association between participation in social activities and functional status was documented in a 9-year longitudinal study with older adults in the US.[49] Another study showed that social disconnectedness and perceived isolation are independently associated with lower levels of self-rated physical health.[50] Furthermore, a strong impact of social integration on recovery from illnesses such as cardiovascular disease and stroke has been

documented.[34,51,52] The impact of social relationships on aspects of mental health, such as psychological well-being and stress reactions, has also been well-documented.[26,53,54] While it was initially thought that this association occurs only through the moderating effects of coping resources and coping strategies, the stress-buffering effect,[54] results of later reviews suggested the coexistence of main effects and buffering effects.[26]

Cognitive well-being

Both compositional (e.g., group membership, frequency of contact between network members, social isolation, (dis)connectedness)[50,55] and functional characteristics of social networks, including social (dis)engagement, social support, and social conflict, have been identified as risk and/or protective factors of cognitive function, ability, and decline.[56–59] More frequent participation in social activities and higher levels of perceived social support[60] as well as having close social ties[61] were associated with better cognitive function among older persons without clinical signs of dementia. Findings from longitudinal studies also provide support for this relationship. In a 7.5-year longitudinal study, social support, specifically emotional support, was found to be a significant predictor of better cognitive function.[59] In terms of social engagement, higher levels of participation in social activities, maintenance of social connections, and frequency of visual contacts with relatives have been found to act as protective factors for cognitive decline among the elderly.[57,58,62] Furthermore, in a longitudinal study of Japanese American men, those who were socially engaged at low levels during midlife and late life were at increased risk for dementia than those who were engaged at high levels, and those who dropped from high to low levels of engagement over time had the highest incidence of dementia.[63] Although it is difficult to disentangle the cyclic nature of the relationships between health status and social engagement (e.g., levels of engagement being influenced by the development of dementia), some of these findings suggest the influence of social engagement on cognitive decline. After reviewing the epidemiological studies, Fratiglioni and colleagues concluded that sufficient evidence supports the notion that active and socially integrated lifestyles have protective effects against dementia.[56]

Relationships Between Social Networks and the Aging Mind and Brain

The pathways through which social networks and relationships influence health and well-being are very complex and difficult to uncover.[64,65] One possible way to investigate the pathways is to look at the compositional and functional characteristics of social networks. Social interactions can influence both the compositions and functions of social networks that can alter individuals' health-related *behaviors* and *perceptions* that, in turn, impact their cognitive well-being. Berkman and colleagues postulate that social networks influence health through functional mechanisms such as social support and social engagement.[66] In terms of the behavioral pathway, it has been shown that social engagement can lead to increased physical activity levels[67] that can facilitate healthy brain aging.[56] Socially well-connected individuals are also less likely to smoke and more likely to eat a better quality diet.[68] For the perceptual pathway, participation in social activity may modify the effects of age-related health changes[69] through providing opportunity to contribute to the society and enhancing social roles and purposefulness in life.[70] It has been shown that increased opportunity for social engagement improves perception of social support availability and reduces feelings of loneliness,[71] and feelings of loneliness significantly predicted IQ at age 79 in a 60-year longitudinal study.[72] In another longitudinal study, an increased level of loneliness was associated with decreased cognitive ability, and this association was partly accounted for by symptoms of depression.[55] Given the strong evidence showing the link between depression and

dementia,[73,74] this may represent another pathway through which social networks influence cognitive aging.

Some evidence also sheds light on the biological pathways through which social networks influence health. There is suggestive evidence for association between social relationships and human immune function.[7–9] In animal studies, social isolation was associated with delayed immune response[75] and development of type 2 diabetes.[76] In terms of brain health, social engagement may improve synaptic activity and efficient brain recovery and repair, thus reducing individuals' risk of dementia.[63] One study documented an improvement in executive functioning through social engagement accompanied by positive changes in brain activity among seniors who volunteered at public schools.[10] Another recent study showed that living alone and having less social support was associated with decreased processing speed.[55] Stress responses (e.g., hypothalamic-pituitary-adrenal functioning) were also shown to be modified by the presence of social support among women prior to their surgery for cancer,[11] and an increase in cortisol production over time led to a decline in memory performance; whereas a decrease in cortisol production led to an improvement in memory performance among community-based older women.[77] Studies reviewed here suggest the existence of multiple pathways through which social networks and relationships may influence health, thus, partly explaining why social relationships influence overall health status rather than specific disease processes such as physical and cognitive decline.[14]

Characteristics of Social Networks and Social Relationships among Older Adults

In early years, Kahn and Riley posited that individuals are influenced by social networks and these networks continuously change as individuals move through various life stages.[78] Antonucci later noted through a review of evidence that the characteristics of the social network do change as individuals age and that these changing characteristics influence how older adults maintain their levels of activity in later life. Bowling also noted the changing nature of social networks as well as the unique network characteristics for older adults and their impact on health status and ability to adapt to the physical, mental, and social changes related to aging. Although there are some inconsistencies in the findings across studies, stronger evidence exists for changes in social network characteristics as people age such as a decrease in the size of social networks, frequency of contacts with social ties, number of ties in close proximity, and level of reciprocity in support exchanges.[15] This emphasizes the importance of not only considering social network characteristics of older adults but also the changes that occur in these systems over time to examine their impacts on health outcomes in later life. Older individuals in the developed society have become especially vulnerable to social isolation due to longer postretirement years, widowhood, loss of friends, illness, residential relocation, and increasing geographic dispersion of family members and friends.[79] In general, older individuals spend less time on social activities compared to younger individuals,[80] partly due to age-related physical, cognitive, and social changes that influence individuals' ability to remain socially engaged.

Older adults are increasingly using electronic tools to stay connected with their family and friends. For example, in the United States in 2012, more than half of older adults were online and 70% of the internet users were online every day to do things like check email (86%) or social network sites (34%)[81] and search for health information (47%).[82] In addition, nearly 70% of older adults own a cell phone[81] and 20% reported having a smartphone that also allows them to stay electronically connected with family and friends[83,84] who may live away from them. How such changes in the way older adults interact with others and the influence of technology on social engagement and well-being outcomes remain underexplored. Additionally, concerns about economically disadvantaged older adults not having the access to or not knowing how to use such

electronic tools, and their increased risk for social isolation due to not being able to adjust to changing nature of interpersonal communication and interaction have been raised.[83]

Compositional features of social network characteristics

Some studies have shown that the *sizes* of social networks of older people are smaller compared to those of younger individuals[78] due to mortality among members and life changes such as retirement and relocation. However, other studies showed that the size of the social network does not change over the life course[85] because lost ties are replaced with new social ties by older adults.[86] Together, these studies imply that individual variations defy simple overall trends. Likewise, while some studies have shown the importance of larger social network size on health,[30,87] other studies show that one or two people in the network can provide the optimal support needed to maintain health and well-being.[33,88] Generally, larger networks provide more instrumental and emotional support,[89] and provide greater opportunity for social interactions and engagement whereas smaller networks may be able to provide more organized support that meets the needs of the individual as network members tend to know and interact with each other. Older adults also have more *homogeneous* networks mainly consisting of family and relatives than younger adults,[15,90] and homogeneous networks bring more emotional and instrumental supports to the members compared to less homogeneous networks.[17] Because of the homogeneous nature, older adults' networks also tend to be *denser* with network members knowing and interacting with each other.[19] Denser networks can lead to higher levels of instrumental support available to members; however, older adults may also experience decreased opportunities for making new social contacts.[19]

Because social networks increasingly contain more family ties and fewer friends as individuals age, the *proximity* to network ties tends to increase,[85] especially when individuals relocate or family members move away. Older adults consider geographic proximity when developing companionships[91] and proximity also influences their access to readily available support.[19] In addition, the *frequency* of contacts with social network ties appears to decrease with age,[92] and the decreased frequency is associated with increased risk for mortality.[93–95] Finally, asymmetries in social relationships increase as people get older, resulting in fewer opportunities for the older adults to give support to others.[78] The *ability to reciprocate* received support was found to be the only structural network characteristic that predicted overall well-being among older adults.[85]

Functional features of social relationships

As discussed earlier, older adults may be at increased risk for losing sources of social support or becoming socially disengaged due to possible changes in their social network composition. Older individuals seem to spend less time engaging in social activities compared to younger individuals.[80] Levels of productive activity also tend to decrease with age, mainly due to a decline in paid work and social participation related to raising children,[96] and this decrease is associated with poorer health status.[97] However, some older adults remain as active as younger people in unpaid work and volunteerism[96] and those individuals tend to show less physical and cognitive decline as reviewed in the earlier section of this chapter. Evidence shows that merely being in a social context was more strongly associated with health than the actual participation in social activity.[98] It is likely that being in the social context not only helps individuals maintain social roles but also provides them with access to potential sources of support when it becomes necessary. Although the evidence points to strong associations between higher levels of social support and better health among older adults,[9,15,46,54,71,99–101] the amount of support received decreases as people get older.[102] Studies showed that perceived levels of social support was a strong predictor of 30-month mortality among older adults in a community, and its predictive value was higher than that of the observable exchange of support.[6,93] Another study also showed a positive impact of perceived support on

well-being without any explicit changes in the actual support exchanged.[103] Because objective indicators of social support (e.g., frequency of support provision) would not reflect individual differences in the needs,[15] it is important to consider subjective measures (e.g., perceived levels of available or received support) in determining what aspects of networks should be enhanced to achieve better health outcomes.

Addressing the Links Between Social Relationships and Cognitive Aging

Interest in promoting social engagement among older adults to facilitate healthy aging is growing. Social engagement not only positively influences the physical, mental, and cognitive well-being of older adults but also allows socially integrated individuals to remain independent longer in community settings.[104,105] As an increasing amount of evidence becomes available in the field, researchers have attempted to translate the knowledge gained into effective intervention efforts.

Although efforts are being made, only a limited number of interventions have been implemented to enhance social engagement among older adults and results have not been consistently positive.[106] Interventions that led to the enhancement of social relationships and integration have involved, for example, providing support in times of crisis,[107,108] organizing support groups,[109,110] promoting community organization among older adults,[23] and facilitating volunteering.[111] Volunteering has been shown to serve as a protective factor for mental illnesses during spousal bereavement,[112] and has a positive impact on self-reported health among older adults.[113] Another study, a randomized trial of a volunteer program for older adults, The Experience Corps®, showed that participation in this program led to increases in social, physical, and cognitive activity among the participants compared to the control group.[114] Furthermore, Carlson and colleagues documented significant intervention effects of this senior volunteer program in increasing brain activity among African American participants who were at increased risk for developing cognitive impairment.[10]

Social Networks of Families Caring for the Aging Mind and Brain

Social networks both influence and are influenced by individuals. The studies introduced above show the potential influence of social networks on individual health; however, social networks are also influenced by individual members including those who may be experiencing age-related decline in physical and cognitive functioning. In this section, the impacts of having an individual affected by dementia on familial social networks are discussed.

In 2013, about 5.2 million people were affected by Alzheimer's disease and related dementias in the US, and this rate is projected to increase to 13.8 million in 2050.[115] Most individuals with dementia (80%) live in the community and are cared for by family and other informal caregivers.[115] Because of the nature of dementia symptoms, family caregivers often face physical, emotional,[116,117] social,[118] and financial strains.[119] For example, informal caregivers are less likely to engage in preventive health behaviors,[120] show lower immune functioning[121] and are at increased risk of mortality.[122] The severity of patients' cognitive and behavioral symptoms influences caregiver well-being,[123–125] and caregiver well-being, in turn, influences patients' well-being[126,127] generating a symbiotic relationship. However, a recent report suggests that more hours spent on caregiving is not necessarily associated with higher mortality and that active participation in caregiving may have positive impacts on caregiver well-being.[128] It is likely that interpersonal relationships and other social network elements also determine how caregiving impacts the health of the patient and family members.

Caregiving creates changes in family relationships and functioning[129,130] that can act as stressors for some family members as they accommodate to provide support and care to the affected

individual.[131] Caregiving impacts each family member differently,[125] and family members engage in caregiving in various ways at various levels (i.e., direct care, providing support to caregivers, sharing household chores, organizing services). Caregiving responsibilities tend to be shared by multiple family members such as adult children, spouses, and grandchildren.[132] Caregivers may also change over time within the family, for example, from spouse to adult children or among multiple adult children.[133] The process of negotiating caregiving responsibilities, or lack of this process, within the family can go on for many years, and family members often experience conflicts as caregiving responsibilities and family roles change,[134] sometimes leading to feelings of anger, resentment, and guilt among family members.[135] Perceptions about inequitable distribution of caregiving tasks within the family has been identified as one of the main causes of caregiver distress[135] and biological family members may especially be at higher risk for caregiving distress as they are often expected to provide higher levels of care within the family.[136] Feelings of anger, resentment, guilt, and distress may influence family members' ability to cope, and can lead to increased depressive symptoms among them.[137,138]

At the same time, social networks provide the context in which family caregivers gain access to support and resources.[139] Dementia caregiving research has predominantly employed the stress process framework[140] and showed that financial resources, social support, and perceived efficacy in care provision are important coping resources for caregivers.[141,142] Caregiving interventions, therefore, have focused on reducing caregiving burden through education, support, and skills training of primary caregivers.[143] However, due to the modest effectiveness of such interventions,[144,145] caregiving researchers are suggesting the need to consider family-level approaches.[146,147] For example, the family's ability to adapt to changes has been associated with continued support provision[148] and the ability to resolve conflicts has been associated with more care provision,[149] thus can be the targets of interventions.

The compositional characteristics of familial networks (i.e., size, demographic compositions) have implications on how families provide care and adapt to the changing needs of family members. For example, women are more likely to provide direct care than men,[150] thus family networks with more females may be more resilient than others in caregiving situations. Similarly, networks with more biological family members may possess more caregiving resources because of a feeling of filial obligation among them.[151] A study showed that proportion of kin and network size were negatively associated with caregivers' family-related distress, and that support availability weakly mediated these associations.[152] The characteristics of network functions such as exchange of support and resources among members have also been examined extensively and shown to be important in caregiver well-being.[20] Network-level interventions such as identifying and activating potential support sources that are on hold[153] or restructuring interaction patterns to facilitate negotiations and to optimize caregiving processes can greatly enhance the well-being of entire family systems including affected relatives and primary caregivers.

Concluding Thoughts: Healthy Aging of our Mind and Brain – Where are we Headed?

Available evidence suggests that social networks and social relationships may have implications on how individuals' mind and brain age through behavioral, perceptual, and biological pathways (Figure 2.1). On the other hand, the way individuals' mind and brain age has implications on the social contexts that surround them. In some cases, challenges associated with providing care to those affected by dementia result in changes in family relationships that determine the outcomes of family caregiving processes and the well-being of the affected individuals and their family. Positive aging of the mind and brain (AMB) can lead to more participation in generative activities among older adults that contribute to the well-being of the society and younger generations.

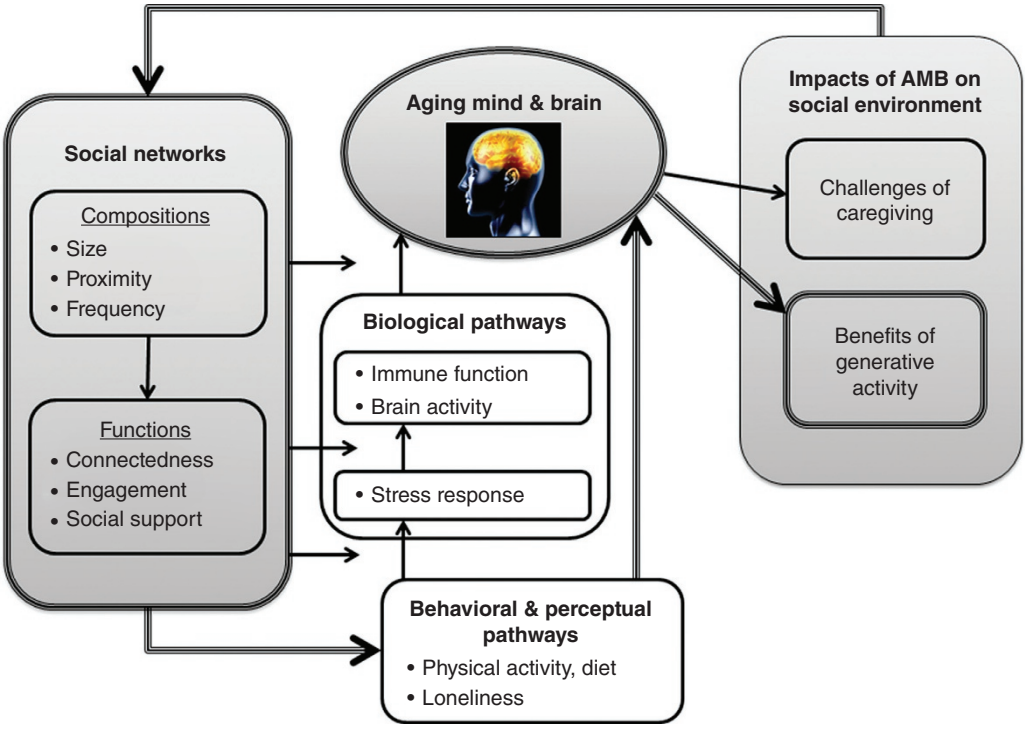

Figure 2.1 Overview of the literature on social networks, social relationships, and their effects on the aging mind and brain.

Any of these associations can be intervened upon to foster social engagement and achieve better health outcomes. The pathways indicated with enhanced lines in Figure 2.1 (the link from social networks to generative activity through aging mind and brain that lead back to enhanced social networks) represent the efforts being made through current community-based interventions.

Attempts to enhance social networks have not always been successful or have not achieved desired levels of change in health outcomes.[154] It is likely that this is due to a lack of understanding of the mechanisms through which these factors influence health and well-being. Traditionally, epidemiological studies evaluated social relationships using such indicators as marital status and number of friends and/or relatives. Using social network size in these studies assumes that the support and influence from each member of the network are all equally effective. However, studies show that the existence of social network ties does not guarantee the availability of social resources such as support, information, and context in which individuals can maintain social engagement.[155] Social network literature clearly indicates that a more detailed examination of social networks, through evaluating compositional and functional characteristics as well as interaction patterns among network members, can greatly enhance our understanding about the way social contexts influence physical and cognitive health.[19] Furthermore, understanding the mediating roles of functional characteristics of social networks will enhance our knowledge about the mechanisms of influence and improve future intervention efforts. Through enhanced understanding of social networks, interventions move beyond opportunities for social participation to identifying specific social relationships that can be influenced, or interaction patterns that can be restructured, to facilitate optimal social network functioning.

There have been dramatic shifts in the structure of social networks in our society as family compositions change due to the extending of life expectancy, fewer numbers of or no children per

household, and increasing rates of divorce, remarriage, cohabitation, and never-married individuals.[156] The geographic proximity between older adults and their family also continues to increase as adult children move away to pursue their career or older adults relocate after retirement. The traditional nuclear family model that includes parents and children or a three-generation household model in which parents live with their adult children and their grandchildren is seen less frequently in industrialized societies. Considering that family members continue to be the most important network members to older individuals, such changes in family systems can put older adults at increased risk for limited social support and resources. Although emotional and informational support may be provided through electronic communication, instrumental support such as helping with shopping and transportation may not be easily provided by the family members living farther away. With such changes, older individuals are increasingly considering their close friends as family or "fictive kin," and these friends function as providers of important social resources such as accompaniment to medical visits, helping in decision-making, and providing instrumental support when family members are not readily available.[157] Therefore, future research of older adults needs to employ an expanded definition of social contexts and family social networks to gain a comprehensive understanding of social relationships.

Similarly, considerations about the role of the internet in social relationships are also necessary. Having access to the Internet allows older individuals to stay connected with family and friends who may not live close to them.[158,159] However, research also shows that having access to the internet and using cell phones reduced the connectedness among older adults with their local neighbors[160] implying a potential trade-off that requires further investigation. More research is needed to increase our understanding about how technology influences social relationships and how it may be useful in facilitating perceived social engagement among older adults. In order to take advantage of technology to facilitate social well-being of older adults, we need to identify potential alternative sources of social support that require in-person contacts such as instrumental support, and ways to ensure access to such technology among all older adults, including those who may be economically disadvantaged and especially vulnerable.

Facilitating social participation through volunteerism appears to be one of the promising intervention approaches to enhance social networks and to facilitate healthy aging. In order to make public health impacts, it is important to involve individuals who have limited social interactions, or are at risk for social isolation. Health promotion programs offered in the community to facilitate healthy brain aging, such as physical exercise or cognitive stimulation activities,[62,161,162] often attract those who are already socially engaged. However, the opportunity to contribute to society through volunteering was effective in motivating participation among those older individuals who normally do not participate in such programs.[114]

The concept of generativity, interest in contributing to the development and well-being of others such as younger generations and the society,[163,164] has been increasingly considered in research concerning the health and well-being of older adults. Many older adults express their desire to be useful and valuable to the society and feel that it is their moral responsibility to provide for others and future generations.[165–167] Those with generative desire tend to engage in more social and productive activities to sustain self-esteem and well-being.[165,166] On the other hand, those who feel low levels of social usefulness experience higher levels of the activities of daily living (ADLs) impairment[168] and mortality, and lower self-rated health.[169] The findings from an intergenerational mentoring program documented the enhancement of academic skills in students along with decreased levels of disability and loss of executive function among older volunteer mentors.[170] Older adults, including those who are dependent on others for care, desire to[171] and are able to participate in volunteer activities to help.[172] Future public health efforts to facilitate healthy aging through social engagement can consider using this concept of generativity to motivate and engage older adults in social activities. For example, asking older adults to share life stories creates an opportunity for generative activity[173] and facilitates the preservation of historical information that benefits future generations.[174] Older generations also have more knowledge about their

family's health history[175] that can facilitate risk assessment and disease prevention among family members.[176,177] Thus, creating opportunity for older adults to share such information can help enhance social engagement among them while bringing benefits to the society and future generations.

As reviewed here, participation in social interactions among older adults is likely to be influenced by the complex interaction of many elements, including physiological, psychological, and social factors. While studies have looked at the influence of physical, psychological, and macro-level sociodemographic factors on participation in social activities among older adults, more studies are needed to investigate the impact of individual social network characteristics and functions on the level of social participation and engagement. Investigating the mediating mechanisms through which social participation may influence cognitive aging will assist health professionals in developing social programs that can effectively and appropriately enhance or maintain the cognitive functioning of older adults. Furthermore, a better mechanistic understanding through which social networks and social relationships influence cognitive aging is needed. Developing a social network framework that will facilitate the identification of biological-, individual-, interpersonal-, and community-level factors that most prominently influence, and are influenced by, cognitive aging will be useful. Once such an understanding is gained, social network assessment tools to help identify the strategies to facilitate optimal aging of the mind and brain through enhancement of social networks and relationships among older adults can be developed.

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3

Aging and the Brain

Veena Prahlad and Madhusudana Rao Chikka

Key Points

- The proximate culprits in aging are likely to be structural, bioenergetics, or functional constraints that prevent an organism from continuously maintaining (actively synthesizing, stabilizing, and renewing) its core macromolecular complexes essential for biological function.
- The evolutionary explanation for aging revolves around the idea of antagonistic pleiotropy, whereby aging exists because of traits that have been selected for because they confer an advantage to growth or fecundity of the animal despite being detrimental to somatic maintenance and prolonged survival.
- Exposure to mild stress, such as caloric restriction, increases longevity, delays aging, and increases subsequent resistance to a lethal stress.

Introduction

It is said that many of the profound aspects of human culture arose from man's struggle against mortality. Yet, while the inevitability of death has accompanied man throughout his history, the rate of aging as seen today, appears to be a more recent phenomenon.[1,2] Comparative biodemography shows that the mortality profile of the hunter-gatherer was closer to that of wild chimpanzees than to modern man in the developed world, with mean lifespans close to 32 years.[3] Indeed, up to only about four generations ago, death from predation and disease was the norm, and mortality rates are thought not to have differed much from what they had been for most of human evolution. However, within recent times, mortality rates have dropped precipitously and all nations are expecting an unprecedented increase in the proportion of individuals over 65 years of age. This increase in human lifespan is attributed to a combination of better management of our health and environment: the reduction of childhood mortality, better control and management of communicable diseases, improving nutrition, reduction in mortality, etc. This decrease in mortality comes with the cost of degenerative diseases of aging. However, notwithstanding the costs, the increase in lifespans achieved within what would not even qualify as a blink in evolutionary time is amazing, and reflects the extraordinary malleability of biological lifespans in the context of environmental influences. Aging, once thought of as a passive, uncontrollable process of deterioration over time with little to no genetic regulation, is today understood to be, instead, a consequence of regulatory mechanisms that actively control how cells, tissues, and organisms respond to their environment[4]. Thus, although the underlying explanation for aging, and the ability of the genome to respond to

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changes in its environment by decreasing or increasing the lifespan of the organism in whose cells it resides, are unknown, studies from model organisms and data from aging wild populations suggests a complex picture whereby cells and tissues of an organism cooperate and compete to modulate the lifespan, healthspan, dysfunction, and ultimate demise of the organism.

Experiments on animal model systems suggest that aging of neurons shares almost all aspects of aging with other tissues, including the remarkable plasticity and malleability with regards to environmental influences. While the nervous system plays a prominent role in controlling the rate of aging of other tissues, it is in turn also influenced by the aging of the soma in complex and interesting ways, offering unexpected possibilities for manipulating the aging of the brain and neurodegenerative diseases of aging.

In our understanding of aging there are some critical features that we need to grapple with, which are hard to define, but easy to recognize. The first, most obvious one is time. Aging is defined as a deteriorative process that decreases the ability of the organism to withstand extrinsic stresses, and increases the probability of dying with time.[4] However, while the continued existence of all organisms increases their probability of death, most organisms age while a few, like hydra, do not.[5] In addition, despite the vast and extraordinary spread of lifespans in the biosphere—with turtles living up to 150 years and adult mayflies living for two hours—chronological time seems to be less impactful to our understanding of aging compared to developmental time, reproductive strategy, the organism's trajectory through varied experiences, ecological niches, and circumstances that make larger contributions to the rate of deterioration of cells and tissues. These latter aspects play important roles in the senescence of all tissues and recorded, in the brain as various aspects of memory, appear to be particularly vulnerable in human brain aging.

The purpose of this chapter is to set brain aging in the larger context of organismal aging, and examine how similar mechanisms drive the trajectory of age-related changes in the brain and body. To do this we will review some of the reasons for age-dependent deterioration of the organism, beyond simple entropy. We then review five cellular changes that are, in many ways, a consequence of chronological time, and review how interactions between cells can alter, reset or accelerate the effects of these time-dependent changes. Throughout the chapter we will emphasize the interactions between neurons and non-neuronal cells, brain and body, to highlight our current understanding that aging as a genetically regulated consequence of how cells and animals respond to each other and their environment (Figure 3.1).

Why do we Age: Evolutionary Theories of Aging

The time dependent deterioration of macromolecules, cells, tissues and ultimately organisms is, no doubt, in part, an inescapable consequence of entropy that governs the chemical reactions which are required for life. However, given that biological systems are not simply conglomerates of macromolecules running their course to decay, but instead are maintained, actively, through energy-dependent quality control and surveillance mechanisms that themselves are repaired, recycled and renewed, the arrow of time is not immediately apparent as an explanation for why cells and tissues senesce. An evolutionarily plausible argument for why senescence—a gradual decline of function—has persisted, was first developed by Peter Medawar in 1952,[6] and later supported by work from numerous others.[7–10] Medawar pointed out that the question was not why natural selection had selected *for* aging. Instead, since natural selection acts on traits that affect reproduction and survival of populations, traits that manifest after reproductive age can be neither selected for or against and are therefore likely to persist post-reproductive age. Thus, according to this hypothesis, senescence can evolve because (a) allelic variations that affect fecundity or survival late in life accumulate in a population due to the absence of strong selective pressure against them, or (b) allelic variations that confer strong benefits to reproduction or survival early in life, but accrue detrimental effects with time, accumulate notwithstanding these late deleterious effects,

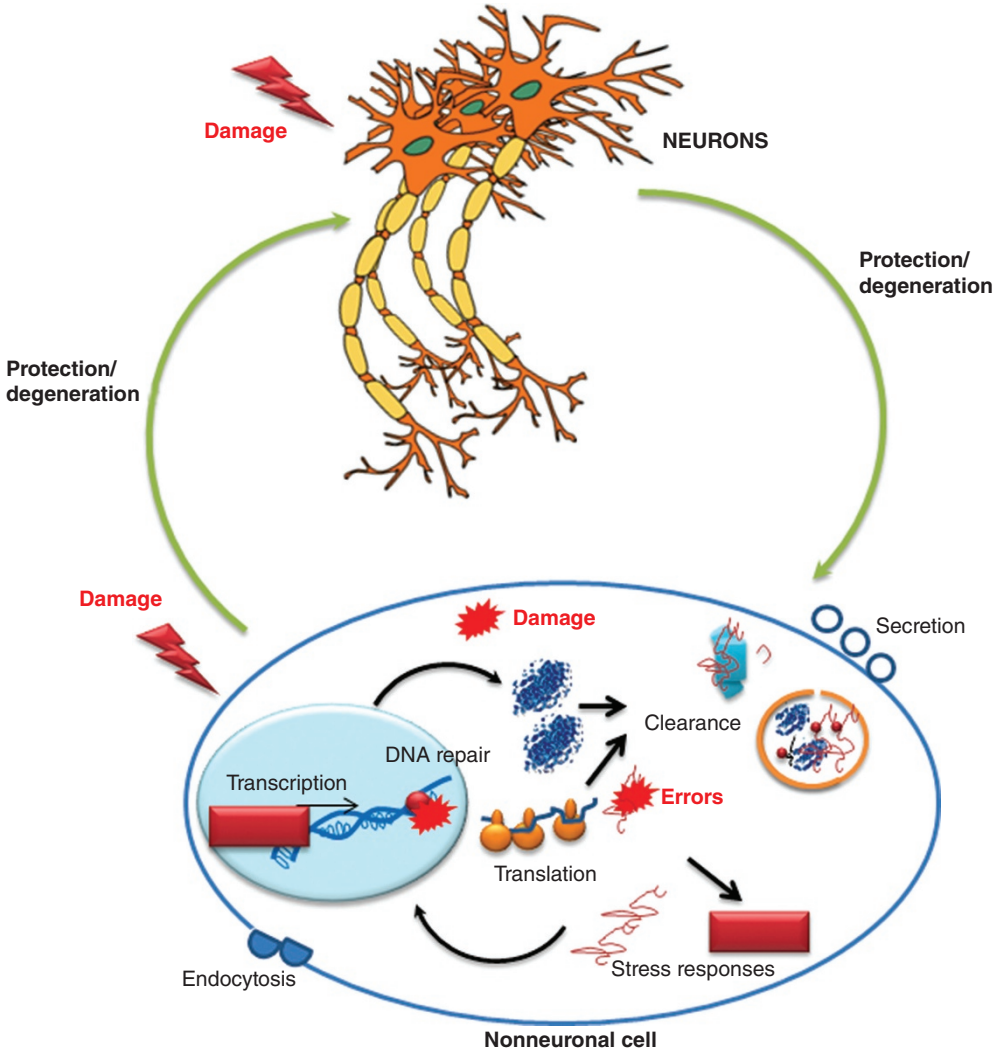

Figure 3.1 Aging is a consequence of regulatory mechanisms that actively control how cells, tissues, and organisms respond to each other and their environment. Neurons control the health and functioning of distal tissue. Distal tissue in turn modulates neuronal aging.

as their early fitness benefits outweigh their later disadvantages. An example of this was the relatively high prevalence of the dominant allele causing Huntington's disease. As suggested by Medawar, Haldane[7] proposed that the declining strength of selection with age might explain why such a disease would not have been efficiently eliminated by selection as individuals in ancestral, premodern populations would already have died well before they could experience this late-onset disease.

The latter evolutionary argument, termed *antagonistic pleiotropy*, offers a robust explanation for the existence of aging and predictions that has been modeled and tested repeatedly in various formats.[8–10] One of the predictions of this theory is that delaying reproduction should lead to the selection for longer life spans, a phenomenon elegantly demonstrated in laboratory evolution experiments in fruit flies.[11,12] Consistent with these experimental evolution scenarios, even in the short term, virtually all experimental manipulations—genetic or environmental—that increase

longevity are associated with a decrease in early-life fitness components such as decreased larval viability, increased generation time, decreased body size, decreased fecundity or brood size, etc. Direct competition experiments between the long-lived mutant nematode *Caenorhabditis elegans* and their shorter-lived parent strain[13] also show that increasing lifespan has fitness costs that result in the eventual dominance of short-lived, more fecund individuals in a population. Decreasing environmental hazards also is a condition that selects for retarded rates of aging and longer life, seen in a "natural experiment" comparing the lifespans of opossums in a low-hazard island population with a high-hazard mainland population.[14] Thus, our current understanding of senescence in animal models and humans is that it reflects evolved limitations in somatic maintenance, most likely selected for due to the benefits they confer to early life fitness, including high fecundity, but which result in a buildup of damage and eventual deterioration of the individual with time.

Cellular Mechanisms that Drive Aging

As mentioned above, the evolutionary theory of aging suggests that the proximate culprits in aging are likely to be any structural, bioenergetics, or functional constraints that prevent an organism from continuously maintaining (actively synthesizing, stabilizing, and renewing) its core macromolecular complexes essential for biological function. An equally plausible culprit could be regulatory mechanisms that respond to internal or external changes by causing a redistribution of resources away from somatic maintenance. These constraints typically depend on the ecological habitat of the organism, and other life history traits such as generation time, size, metabolic needs, availability of food, cellular and tissue organization, and interaction with its environment. However, despite the remarkable variation in lifespans and life history traits, the proximate causes of aging of cells and tissues share common features.[15] As aging is the result of a complex interplay among various biological processes, the biological processes that are considered the drivers of aging are not only those that manifest during normal aging, but those whose experimental modulation can accelerate or decelerate the rates of aging in model organisms. These processes are briefly described below.

Genomic instability

Despite the many mechanisms dedicated to the repair of DNA damage, the accumulation of genetic damage is a common feature of aging seen in model organisms as well as humans.[16] Somatic cells are continually exposed to environmental mutagens such as UV radiation, or toxic chemicals. Biochemical reactions and respiration themselves result in the formation of reactive oxygen species which damage DNA. Finally, chromosome segregation, DNA replication, and even DNA repair enzymes are error prone, guaranteeing that, with time, cells accumulate enough genomic alterations that could render them and the organism dysfunctional. Although it is difficult to unravel whether the accumulation of damaged DNA within cells over time is the cause or consequence of aging, increased DNA damage due to hereditary mutations in genes involved in DNA repair leads to premature aging syndromes such as ataxia-telangiectasia (A-T), Werner syndrome, Bloom's syndrome, etc. Experimental detection of random low-abundance genomic alterations are difficult, and the first systematic studies to conclusively demonstrate an increase in DNA damage with age were conducted in experimental model systems such as *Drosophila melanogaster,* using an elegant method where a *lacZ* reporter gene integrated into specific loci of the organism served to read out mutational rate.[17] These experiments showed an age-dependent increase in mutations in the *lacZ* gene. They also revealed that the increase in mutations was dependent on environmental conditions such as temperature and were tissue specific. For instance, while mitotic tissue in the abdomen accumulated less than a twofold increase in mutations between

young and old flies, cells in the thorax accumulated over three times more mutations in the same duration. The same tissue showed a higher amount of DNA damage when the organism was raised at a higher temperature. These studies suggest that cell-extrinsic features, and tissue-intrinsic features, such as different sensitivities of repair mechanisms or increased metabolic activity, collude to result in the amount of age-dependent DNA damage. Similar results were obtained in experiments on mammalian model systems.[18]

In all tissues, DNA damage in the form of single- or double-stranded breaks and DNA adducts initiate a molecular response to repair DNA, or in many cases, activate apoptosis. The DNA repair machinery present in all cells consists of highly conserved sets of enzymes that continuously monitor genomes for DNA damage and are responsible for the high integrity of the genome under physiological conditions. Repair mechanisms include nucleotide excision repair systems (NER) that remove bulky adducts that are incorporated into DNA; base excision repair (BER) enzymes, an error-prone ligation mechanism; nonhomologous end joining (NHEJ); and homologous recombination. Amongst these pathways homologous recombination is the least error prone and high fidelity mechanism as it uses a homologous sequence to template the repair of DNA. Other repair pathways do not use homologous templates and are more error prone.

Within the nervous system, too, appropriate responses to DNA damage are required to maintain homeostasis and prevent disease. Human syndromes, such as A-T that results from defective responses to DNA damage, often feature overt neuropathology. As with all mitotically dividing cells, neural development is a critical period during which cells can accumulate mutations due to the errors in replication and repair of damaged DNA templates. The adult nervous system, however, is also likely to continue to accumulate double-stranded DNA breaks given the brain's large oxygen consumption, high metabolic rates, and the generation of reactive oxygen species (ROS). Recent studies have shown that in rodents, natural behaviors such as exploration of a novel environment causes DNA double-strand breaks (DSBs) in multiple regions in the neurons of young adult mice.[19] In addition, being postmitotic, neurons depend on the more error-prone repair NHEJ mechanism for repair of double-strand breaks.[20] There is evidence that the DNA repair enzymes themselves do not function efficiently with age. For instance, cohesive end joining activity decreases with age of the animal, with expression of other DNA repair enzymes.[21] DNA damage response signaling itself is also reduced with age.[22] The lack of faithful DNA repair mechanisms seems to be particularly evident in the case of age-related neurodegenerative diseases, and several studies have shown that neurons accumulate more DNA damage in human neurologic disorders compared to age matched controls. Thus, DNA strand breakage is twofold higher in the Alzheimer's disease (AD) cerebral cortex[23] and in the substantia nigra of Parkinson's disease (PD) patients,[24] compared with age-matched controls. However, despite these data, it is still unclear how and whether the random and stochastic accumulation of somatic mutations that might increase in neurons with age as a consequence of inefficient repair mechanisms contribute to the more stereotypic changes in neuronal function and phenotype that occur with age.

Telomere attrition

In contrast to the random nature of mutations, the more consistent shortening of telomeres, ribonucleoprotein complexes that cap eukaryotic chromosomes, has provided a powerful concept for the time-dependent senescence of somatic cells.[25] It has long been known that cells and unicellular organisms undergo replicative senescence, that is, they cease dividing after a certain number of cell cycles. This mitotic limit, or the Hayflick limit, is a consequence of the end replication problem faced by all mitotically active cells due to the fact that DNA polymerase can only synthesize a new strand of DNA in the 5'→ 3' direction. Mammalian somatic cells do not express telomerase, the enzyme required to actively maintain the length of telomeres. Thus telomeres typically shorten with age in mitotically active somatic cells providing a limit to the number of cell divisions these

cells can undergo. Stem cells and germ cells do express telomerase, and can replace the telomeres lost with every cell division, escaping replicative senescence.

Experimental manipulation of telomere length in mouse model systems has provided a causal link between telomere length and organismal aging. Mice with experimentally shortened or lengthened telomeres have decreased or increased lifespans respectively.[26,27] Remarkably, while telomerase-deficient mice show premature aging phenotypes and untimely tissue degeneration, these phenotypes can be reverted in aged mice by experimentally reactivating telomerase.[28] Recently it was shown that chronic psychological stress, a condition that has frequently been correlated with the earlier onset of age-related diseases can result in lower telomerase activity and shorter telomere length in adult women.[29] Telomere attrition also affects other cellular systems such as mitochondria. In telomerase-deficient mice the p53-mediated repression of PGC-1α and PGC-1β causes decreased mitochondrial biogenesis.[30] This mitochondrial decline also occurs during physiological aging in wild-type mice and can be partially reversed by telomerase activation.[31]

While there are strong links between telomere attrition and organismal aging, given their post-mitotic status the aging of neuronal cells appears not to be directly affected by telomere length. Studies in rats indicate that, while the percentage of short telomeres increased with age in the kidney, liver, pancreas, and lung of both males and females, telomere length did not change significantly in brain tissue itself.[32] Consistent with this, Werner syndrome patients that exhibit premature aging as a result of telomere dysfunction display an accelerated senescence phenotype in mesenchyme-derived tissues, but not in neural lineages. Remarkably, in recent studies while reprogramming Werner syndrome patient fibroblasts to pluripotency elongated telomere length and prevented telomere dysfunction, redifferentiating them to mesenchymal stem cells reasserted telomere dysfunction, whereas differentiating them to neural stem/progenitor cells did not.[33] These studies suggest that instead of being the causal effector of aging, telomere length could serve more as a read out for aging. Indeed, although controversial, leucocyte telomere length (LTL) has been suggested as a surrogate marker of telomere length in other tissues/organs, and therefore a biomarker of aging, even providing a readout for neuronal health.[34] Shorter LTLs are evident in patients with age-related diseases such as diabetes, cardiovascular diseases, and neurodegenerative diseases.[35] In summary, these data suggest that telomere attrition is typically thought to affect neuronal tissue by affecting the proliferative capacity of adult neuronal stem cells, and telomerase-deficient mice show deficits both in proliferation in the subependymal zone (SEZ) and neurogenesis in the olfactory bulb yielding reduced numbers of neurons and also underdeveloped dendritic arbors.[36]

Mitochondrial damage

Numerous lines of arguments link mitochondrial dysfunction with aging. Mitochondrial DNA (mtDNA) is compact, and encodes critical subsets of gene products of the electron transport chain (ETC) required for oxidative phosphorylation. Thus, most mutations that affect mtDNA have consequences for the respiratory function of cells. Respiratory function of the mitochondria is, in turn, linked with the production of ROS, the abnormal increase of oxidative stress, metabolic imbalances that can be expected to lead to cellular damage accumulation, respiratory deficiency, and decreasing the amount of adenosine triphosphate (ATP) required for functioning of the tissue. All these impairments are chronic, and the consequences can accumulate over time, plausibly causing age-dependent tissue degeneration and dysfunction. Since, mtDNA lacks protective histones and it is thought that mtDNA repair enzymes are limited, the frequency of mtDNA mutations are thought to be higher than that of the nuclear genome.[37] However, while mtDNA is particularly susceptible to mutations due to the oxidative microenvironment of the mitochondria, mtDNA circles divide and assort independently and cells can contain numerous mitochondria each with a