Open Journal of Geriatrics

Volume 1, Issue 1, 2018, PP: 33-72

Meta-Trends in the Holistic Care of Older Adults

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Abstract

This paper introduces trends in clinical practice and technologywhich impact the way we approach work with older adults. The population over age 65 is not merely an aged mirror of its younger self. Instead, the aging adult is impacted by variables which can alter the trajectory of aging and quality of life. Based on our holistic model of the treatment of older adults, we address 10 trends in aging: brain complexity, epigenetics, biopsychosocial modeling, new approaches to understanding aging, cardiovascular health, lifestyle, prevention, precision medicine, therapy, and purpose in life. Emphasized is the impact of changes in lifestyle behaviors to promote longevity and quality of life. Each factor is examined based on its ability to address the needs of geriatric medicine. These trends influence our ability to change the future of geroscience. We discuss these trends within the context of clinical care with older adults and the potential applications of these advances.

When broken down into factors which impact health, it has been demonstrated that genes account for approximately 30% of variation in health outcomes and behavioral patterns account for 40% (McGinnis et al., 2002). The remaining 30% involves environmental exposure to toxins (5%), social circumstances (15%), and health care (10%). This has been updated and the estimates are roughly the same (Lyubomirski, 2008). In other words, the behavioral and social determinants of health account for most of what impacts health while genetics are less prescriptive. Said another way, aging is not a causal variable. Rather it is a marker on a temporal axis along which various exposures and disease processes operate. Aging then is not a meaningful explanation for why one might experience decline, especially cognitive decline or impairment. Dementia itself is a non-event. It is an end stage of a process of a "brain at risk," a poor accumulation of health, behaviors, and genetics. Both genetic factors and health-related behaviors then influence the functional quality of life and survival to old age.

Longitudinal cohort studies demonstrate that lower levels of cardiovascular risk factors measured by midlife or early older years predicts survival and healthy survival to 85 years of age and beyond (Hyer, 2014). But it is also true that longevity has been observed to cluster within families so that parents and siblings of centenarians have a greater likelihood of attaining advanced age. An offspring of centenarians may even have a delay in age-related diseases. At the other end of the spectrum, about 133 million Americans suffered from at least one chronic disease and it is estimated that this will increase to 157 million in 2020. About 50% of these people will have multiple chronic conditions and each year seven out of ten deaths are the result of a chronic condition (Hyer, 3014). In this context we need to know what aging is and how it unfolds.

There is then paradigm shift in the care and understanding of older adults. We provide some context for this change in the form of a model and discussion of met-trends. This applies to psychopathology as well as the aging process itself. In effect, we are beset with several newer meta-trends that interact with and complicate simple answers. Aging people lose gray and white cells but are good compensators who can alter, to some extent, the onset of and course of dementia. Mild cognitive impairment (MCI or mild Neurocognitive Disorder) is a now teachable moment, not a death sentence. Despite the inevitability of the impact of time, humans are living longer and longer. Life has taken a turn. These trends helped guide development of the Watch and Wait model (Hyer, 2014), described here.

Background

In our current work "Treatment of Older Adults: A Holistic Model" (Hyer, in press), we articulated a Watch and Wait model of care and posited that there are five core domains necessary for understanding the psychosocial phenomena of older adults. These include health, cognition, depression, anxiety and life adjustment. These domains were considered necessary and most often sufficient conditions that, if assessed and addressed, lead to best care. Each person therefore received a profile on each area of No Problem, Mild Problem, and Problem.This profile provides a template for care. In recent years there has developed a dramatic change in the understanding and treatment of older adults, especially where mental health is concerned. We provide one model.

As background, the efficacy of psychopharmacological and psychological approaches is minimal. In truth, the usual pattern of results involves a "response" to a problem, not a remission. Implied is that the utility of a psychiatric classification in determining the course of treatment is poor. In fact, psychiatric/psychological care is more complicated than medical care and any response needs more than traditional, non-holistic care. A Watch and Wait model based on case formulation, more time in assessment, and the application of care rubrics (on each of the five domains), paying less attention to the nuanced differences in treatment (one antidepressant vs another, one psychotherapy vs another, medication vs psychotherapy), but,more attention to the whole person and their complicated world, is seen as more effective.

Due to the complexity of patients, the normal application of empirically supported therapies (ESTs) and the nuances of the research and use of predictor variables in care, while helpful, are not robust enough to warrant allegiance beyond just some respect. We maintain that the differences between one antidepressant and another, one psychotherapy and another, or one medication versus another help providers only at the margins. Published reports suggesting that attending to novel "significantly better," or "evidenced-based," will result in better patient outcomes, is helpful, but doing so with older adults often diverts attention from the real world issues, and has only marginal evidence of benefit. We believe in a comprehensive algorithm for treating more than one problem in older adults is more important (Thielke, Vannoy, & Unützer, 2007).

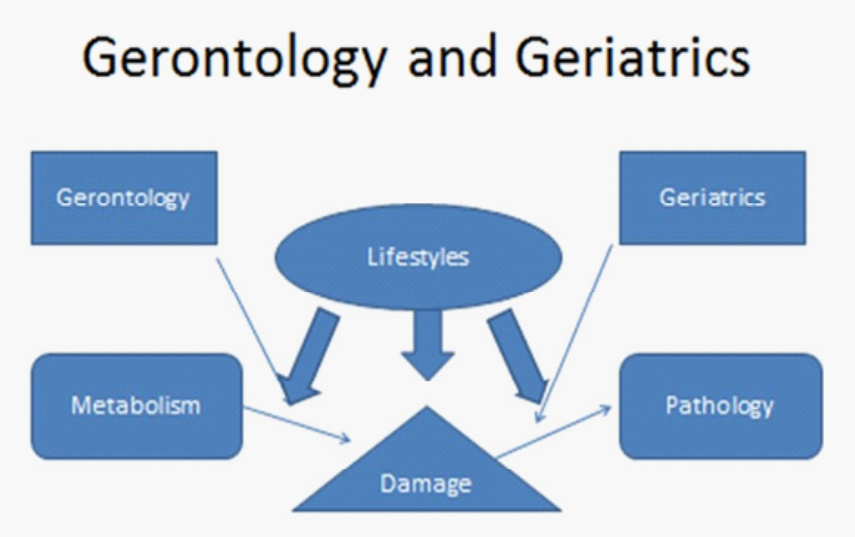
We now know more about aging itself. Biological aging is largely determined by the internal biological clock and accumulation of insults through living. Where the lifespan of the organism is closely related to the biological aging, individual longevity is always a function of specific environmental circumstances, the accumulated insults. The two operate at every level of the bio-hierarchy – genes, proteins, cells, organs, and organisms. As we shall see, epigenetics reigns as it accounts for change in gene expression that is not mediated by mechanisms of the DNA. Again, we are best considered products of a biopsychosocial model where there are varying levels of physical, cognitive, emotional, behavioral and environmental factors that contribute the formulation of the older person (Andrasik, Goodie, & Peterson, 2015).

The complexities of the psychosocial variables responsible for better later life issues are now more readily apparent. The realistic constraints of living into later life make outcomes worse for older adults. Health now rests on our daily behavioral routines. We believe that the biomedical model is reductionistic in this perspective. We only have to note that over 90% of people over 65 take some form of medication and psychiatric drugs exceed all other mental health costs. Most older adults have a chronic disease, which is the cause of seven out of 10 deaths. Compared to other age groups, older adults have the highest numbers of doctor visits, hospital stays, and prescription medication usage. Left unchecked, healthcare expenditures will likely rise from the current level of ~15% to 29% of gross domestic product (GDP) in 2040. The plethora of problems fulminate around the older adult, including the unbearable combination of our five domains -- physical illness, medication side effects, cognitive dysfunction, psychiatric conditions, functional loss, social loss, and inability to afford the medication at full dosing and poor later life beliefs (Cogbill et al., 2010).

Older adult problems are essentially fragmented and meaningful intervention can be the glue for personal and group coherence. The health care

provider becomes an ethnician, translating real life problems with values and goals into hoped-for maximization of function. The ethical parameters of autonomy, beneficence, justice and non-malfeasance remainnecessary to assists in a new paradigm of care. Good care in later life is a creative admixture of common sense, perhaps as deliberated by ethics, and science. In some ways it is more a philosophical or psychological enterprise than a disease process.

In this paper we provide the backdrop for the Watch and Wait model upon which the care program is applied. This understanding involves both gerontology and geriatrics (below). The slow alteration in the accommodation and assimilation of life is first attached to the elements of gerontology, the element of care that is based on awareness of the components of good living, meaning that the epigenesis of culture and psychosocial factors impact the phenomenology of living. This is most influenced by lifestyle. Health care providers need to give respect to both gerontology and geriatrics: Homage to the latter masks the subtle power of the former. Gerontology leads the way. Aging is the result of an ongoing metabolism that collects insults and degrades because it becomes less efficient at house cleaning. Inflammation, oxidation, impaired immune reactions and the like become enemies of cells. Intra-cell and extra-cell damage occurs. Amyloid and tau, the building blocks for plaques and tangles, are often the result. Gerontology impacts the pre-processes for damage and geriatric does the tertiary cures when possible. But the factor that activates change is lifestyle. It is best done at mid-age and continuing, but is helpful at any age. Gerontology is the biopsychosocial dynamic of life; geriatrics is secondary prevention, fixingits maladies. The dynamic for both is to optimize the culture of positive living and growth. Yes, age and disease eventually win out but this interaction can be slowed and softened.



METATRENDS

To put this effort into context, we examine 10 trends applicable to the clinical status of older adults. As noted, they set the stage for the Watch and Wait model. They include : brain complexity, epigenetics, biopsychosocial modeling, new approaches to understanding aging, cardiovascular health, lifestyle, prevention, precision medicine, therapy, and purpose in life. While many researchers are seeking new ways to combat aging-related issues one at a time, experts in the field of geroscience are uniting to develop preventive and therapeutic approaches to fight multiple diseases. Using the Watch and Wait Model, patients can be assessed and treated based on their unique unfolding comorbidities and life circumstance. In the past, heuristics have guided treatment planning. This is not a complete deviation from that model, but instead combines the previously used heuristics to address uniquely interacting physical, social, and emotional factors. In examining recent trends in geroscience, we believe seven offer unique promise in understanding this unfolding of factors:

- Individual and the environmental stressors affect our physical and psychological well being over time.
- Genetics, how our environment can affect gene activity.
- Inflammation, the body's natural response to a range of conditions, though chronic inflammation plays a contributing role to accelerated aging and chronic disease.
- Macromolecular damage, the causes and effects of damage over time to the large molecules that comprise our bodies; DNA for example, which drives the development of chronic disease and age-related conditions.
- Metabolism also is a factor. Metabolic changes due to aging may play a role in cardiovascular problems, neuro degenerative diseases, diabetes, cancer, and other chronic conditions.
- Proteostasis is the house keeping process that regulates and maintains the proper protein function within ourselves.
- Additionally, stem cells and regeneration have been noted. The adult stem cells in our bodies are well-known for their ability to divide, renew, and replace damaged tissue in the body itself.

Using these advances in thought to guide this review, it is crucial to understand that aging is the largest risk factor for most chronic diseases, including stroke, heart disease, diabetes, arthritis, metabolic syndrome, blindness, and frailty, to name the most common. No longer are humans primarily dying of communicable diseases but instead chronic, and at times preventable, disease. Aging may be a modifiable risk factor, relative to chronic disease. As we have suggested care for the aging utilizes much of the total health care spending and is reasonably expected to rise. If aging can be addressed as a modifiable risk factor, increasing lifespan and quality of life even minimally, the burden to healthcare could be exponentially reduced. We address the more salient of these factors impacting quality lifespan here:

Brain Assistance and Complexity

Due to the complexity of the questions being addressed, no single researcher's efforts have provided a panacea to this point. The BRAIN Initiative, a White House Grand Challenge involving more than 100 laboratories in the United States, is attempting to unite and establish nationally relevant neuroscience goals while also developing more universally used assessment tools (Martin & Chun, 2016).Instead of a center-based approach, this group believes that these questions can be addressed most effectively through highly coordinated, multi-investigator, cross-disciplinary efforts which utilize advances in technology as well as thought. Recent advances in investigative technologies, such as connectomics, the systematic reconstruction of neural circuits, as well as neural mental probe systems, new resonance imaging techniques, and computational data mining, offer new insights for exploration. Advances in PET imaging of tau tangles has led to new understanding of radioligands. Tau imaging is an exciting advance and has the potential to redefine the way clinical trials are created and conducted, becoming a useful tool for diagnosis and tracking both disease progression and modification. The typical pattern of tau accumulation occurs slowly, beginning in the medial temporal lobe, increasing asymptomatically over time. However, when beta-amyloid joins the party, the buildup rate increases and tau spreads to the temporal cortex. These new tau imaging techniques maybe able to provide insight into this complex process which is not expressed clearly on current imaging and cognitive assessment measures.

Advancing technology does offer new means of measurement, though large scale, multi-site research efforts are the bread and butter of geroscience trends. During the Rush Memory and Aging Project and the Religious Order Study, 3000 older adults were tracked over 2 decades. Upon autopsy it was discovered that the physiological deterioration of extensive cellular damage, which were thought to define functional decline, did not in fact predict decline (Bennet, et al., 2018). Instead, the opposite was found with cognitively intact individuals showing extensive extracellular damage and those with significant cognitive decline showing less degeneration. There was then a disconnect with cellular pathologies and cognitive decline. Other work has implicated the value of behavioral efforts, finding that factors such as exercise, social interaction, conscientiousness,

and sense of purpose, promote cognitive resilience (Wilson et al, 2013). The authors also note that, even if successful, standard medical care for Alzheimer's disease (AD) is helpful for only about one third of age-related cognitive decline problems. Large scale genomic, proteomic, and epigenomic studies are required for more direction and help.

Two notable differences in the new criteria related to brain degeneration are relative to AD criteria originally published in 1984 include the incorporation of underlying disease biomarkers relative to AD in assessment and treatment (atrophy identified at structural MRI, fluorodeoxyglucose (FDG) hypometabolism and beta-amyloid at PET imaging, concentration of tau in cerebrospinal fluid (CSF), concentration of beta-amyloid in CSF), and the formulization of different stages of disease(preclinical AD, MCI, and dementia). In recent years there are several drug trials in pre-symptomatic patients. The Alzheimer's Prevention Initiative, Autosomal-Dominant Alzheimer's Disease Treatment Trialare testing anti-amyloid drugs in subjects with strong genetic risk factors for AD. Other trials include the Dominantly Inherited Alzheimer Network Trial, the ApoE4 Treatment Trial, and the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Trial which examines anti-amyloid treatment in subjects who are cognitively normal but have imaging evidence of beta amyloid brain plaques. In 2014 alone, virtually all drug compounds investigated in clinical trials resulted in failures. Aducanumab, levetiracetam, a nasal spray of insulin with anamides (antioxidant), and ultrasound (clear toxic clumps) have been reviewed more positively (Small & Greenfield, 2015). The cholinergic hypothesis has been tested because other populations of noncholinergic neurons have been prone to neuro-degeneration. Amyloid and tau theories are suspect also as in both cases APP (a known precursor for amyloid) and tau protein are virtually ubiquitous features of all neurons; hence we need to identify a constraining additional feature that would explain the vulnerability of certain neurons. Regardless we know that pathology is not destiny.

Small and Greenfield (2015) iterated these difficulties througha context of current and future treatments and examining the markers of dementia; presenile dementia, rare mutations, cholinergic deficits, ApoE4, beta and tau. They cite the primary issue in psychopharmacological intervention as the lack of discovery of an underlying mechanism of neurodegeneration. No disease modifying drug or symptomatic treatment has been discovered. The drugs that target tau orbeta amyloid may help symptomatically, but the underlying mechanism is mysterious. Theories implicating amyloid or tau do not account for frequent co-morbidity with Parkinson's disease orthe selectivity of cells that are prone to degeneration localize in the basal forebrain, midbrain, and brainstem nuclei. As these cells have different embryological origins, subsequent neurodegeneration could then be an aberrant form of development. Lack of an exemplary animal model makes researching this more challenging.

It is troubling that we do not yet know the best molecule for target in Alzheimer's disease (AD), for example.As previously noted, biomarkers in the CSF or saliva do not directly reflect the brain disease process. Clinical features of AD are non-specific and cannot be easily assayed until death. Neuroimaging provides information and the common features like the atrophy of the entorinal and hippocampal volumes (especially with an Apoe-E4 allele) suggests a heightened risk, but regional brain changes can have any number of causes. fMRI and PET are the key scans for detection of neurodegenerative problems. Combining other factors like genetic risk factors (APOe allele) with scans (FDG-PET) can increase detection. The Pittsburgh Compound B as well as florbetapir are also helpful. Detection is only one step in this process.

Despite the large variety of compounds available as candidates for therapy, their mechanisms of action are limited to alterations subsequent to disease process initiation; general neuronal health, conventional receptor agents, tau hyperphosphorylation and amyloid. That said, the timeframe for someone experiencing cognitive problems to MCI and then dementia can be as long as 15-20 years. Few studies have follow-up data covering the entire disease process due to time and economic constraints. The longevity of disease progression confounds interventional measures. What appears, therefore, as negative results in the short term could translate into positive benefits much later in time, particularly if participants continue to actively engage in material provided in interventions.

In one of the more important studies on the transition from MCI to dementia, Biomarkers for Older Controls

at Risk for Dementia, BIOGARD, was conducted (Albert et al., 2011). This involves a combo of evaluations; cognition, brain structure, brain proteins. Biannual CSF punctures, MRI, clinical evaluations and cognitive testing were conducted over 17 years. Results showed that at baseline lower A-beta and higher tau, lower right entorhinal cortex and lower hippocampal volume were associated with onset of AD. Cognitive measures of paired associates and symbol digits were also in the mix. Additionally, Hammes, van Eimeren, and Drzezga (2016) studied 10 subjects with AD who had PET (F-18 FDG and Pittsburgh B-11) for both tau and amyloid. Results revealed that tau is directly associated with hypometabolism (reflecting neuronal dysfunction): Nothing for amyloid. Tau is more closely related to neuronal injury; amyloid provides data many years ahead of the onset of symptoms.

In previous work (Hyer, 2014), we emphasize the use of the brain as a metaphor with an anchoring in psychopathology. The brain is complexly present and increasingly understood in the context of the aging process as well as neurodegeneration. As the brain is now known as a set of information processing circuits instead of isolated neurons or functional regions, understanding neurodegeneration, cognitive and physical decline, and problems experienced with aging requires an information flow perspective. Brain disorders then are not deficits in one brain region but a problem of information flow across circuits. Deep brain stimulation (DBS) is a good exemplar of this circuitry model and serves as a guide for future interventions. Problems isolated to CNS abnormalities, including generalized brain atrophy, small vessel disease, cerebral infarcts, Lewy bodies, neuritic plagues, neurofibrillary tangles, and white matter hyperintensities, are common in older adults who do meet criteria for clinical neurological disease. Each of theseindividually or in combination may adversely affect motor function and gait, implicating the system.

Emphasizing this point, 47 million people have amyloidosis without clinical symptoms with one out of seven progressing to AD (Brookmeyer, 2017).This indicates amyloid positive status is risk for AD. Based on a math model from Mayo on 1541 subjects, 3% of normals segue to amyloidosis every year. Progression is fairly consistent: amyloidosis at 60 and AD at 75. In a related Alzheimer's Disease Neuroimaging Initiative (ADNI) study of 243 Amyloid- and 202 Amyloid+ participant found similar trends (Sperling, 2011). All were participants normal at the initial assessment (mean age = 74: education =16 years). In 3.1 year, a summative score (Sum of MMSE, CDR, Logical Memory Recall (PACC) revealed that Amyloid+ participants had higher likelihood of cognitive decline. Having an APO-E4 was greater in Amyloid+ participants. Amyloid may be a bell-weather and not a benign phenomenon or reflector of normal aging (20 years before onset of dementia) (Donahue et al., 2018).

The brain then is the organ of optimal interest in understanding the aging human, with more questions than answers about its function and impact on the process. In regard to biomarkers, we do not know the ultimate molecule(s) for evaluation. It seems weekly that we are finding new molecules for possible targets for an arrest of AD or PD.

Epigenetics

> "There is now a vast amount of data demonstrating the relationship between gene expression and anatomical features in early brain development… we suggest that similar genetic and epigenetic mechanisms continue to impact the structure and function of the brain throughout life…Late in life, similar genetic mechanisms may be involved in the breakdown of brain microstructure, AND changes in experience, as in early development, can advance and ameliorate the deleterious effects of aging. Data from multiple laboratories around the world suggest that calorific restriction and environmental enrichment can impact on gene expression in the aging brain…"
>
> Huffman, 2012, p 9

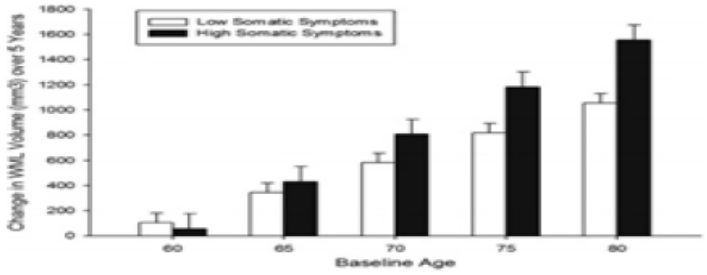
Where the lifespan of the organism is closely related to the biological aging, individual longevity is always a function of specific environmental circumstances, accumulated insults. Epigenetics is the term which represents this phenomenon: biological aging is largely determined by the internal biological clock and accumulation of insults. Said another way, it is an interaction of organismic lifespan and individual accumulated insults. Epigenetics then, as noted above, can be defined as the study of changes in gene expression that are mediated by mechanisms other than DNA. They shape the environmental influences on brain and behavior.

The possible interactions and outcomes involving connecting genes, environment, and epigenetics are numerous. One example, because epigenetic regulation controls when and where genes are expressed, a mutated gene that could cause disease is irrelevant in the context of a normally low expression. However, that mutated gene may have adverse biological consequences if that context changes due to epigenetic modifications resulting from age or exposure, a change in susceptibility. Said another way, in one environment a gene of normally low expression rate can be expressed but in a different environment it is suppressed: the age by gene or exposure by gene interaction that would be mechanistically explained by epigenetics.

At a more basic level we can see changes over time or development. Demonstrating the impact of early trauma, researchers at the University of Rochester examined children's cortisol levels over 3 consecutive years in 201 low-income mother-child pairs(Suor et al., 2015). They found that exposure to specific forms of family adversity when children were 2 years of age predicted the cortisol profile, which in turn was linked to notable differences in children's cognitive profile at age 4. Similarly, a study showing the impact of poverty on brain structural development involved a 6-year longitudinal study of 389 economically diverse children and young adults between the ages of 4 and 22(Hair et al., 2015).They found that children who came from families below the poverty line showed differences in brain structure from middle class and higher income children. Specifically, children from poor families had differences in the brain areas most crucial for academic development, including the frontal and temporal lobes and the hippocampus. The poorer children also had less brain matter overall than the other children.

Brain development extends over a lifetime. A study by Kirton et al. (2014) showed changes in white matter lesions (WML) over a five-year period for different age cohorts. Normal subjects were asked to rate depression or somatic problems on the CES-D at one point in time for their age cohort and measured in WML volume. Five years later they were assayed on WML volume, as seen in the table below. Subjective complaints of high somatic symptoms may predict WML volume 5 years later. This trend was consistent for all the ages studied and extended to the depression ratings.

FIGURE 3. **Change in WML volume over 5 years as a function of the Somatic Symptoms Subscale of the CES-D. Bars represent difference scores computed from estimated values at baseline and in year 5. Low Somatic Symptoms: lower three quartiles of scores (0—4); High Somatic Symptoms: upper quartile of scores (5+).**



Note: Age groupings are for visual representation; age was analyzed as a continuous measure in all statistical analyses.

Kirton et. al, 2014

The usefulness of these finding is considerable. First, there is clear indication that cognitive decline is not due to chronological age per se, but rather is the outcome of multiple causal factors from a broad range of biological and physical health domains that operate along an age continue. This, therefore, provides many opportunities for intervention. Functional biomarkers include many measures, such as index functional capacity, decline with age, fitness, health conditions, and cognitive markers. In addition, objective biomarkers such as histopathological accounts of plaques and tangles, oxidative stress markers derived from biochemical blood assays, genetic markers such as the ApoE4, WMHs, whole brain atrophy, dopamine receptor binding, and amyloid burden, afford additional factors contributing to the concept of *bio-age*. The bio-age of a person, therefore, might be very different, having nothing to do with one's chronologicalage. Two individuals who are 75 years of age who have different biological and functional biomarkers therefore are distinct people and have a different bio-age.

This can be seen in a subgroup of the aging population, labeled "superagers"; youth-like older adultswho respond on assessment like younger adults and have good neurobiology. Superagers make up less than 10% of the older population. Importantly they do not compensate or apply less efficient brain strategies (less dedifferentiation). Normal older adults have different mechanisms. They compensate, have poorer memory, have a default network dysfunction, possess regional specific gray matter loss, and use frontal lobes more. According to Reuter-Lorenz and Park, (2011) twocore areas of brain efficiency at later lifeare in play:the juxtaposition of neurophysiological decline (e.g., gray matter loss) and efficiency of scaffold networks (more frontal lobe activation) results in behavioral outcomes noted in studies. In effect, the normal aging brain declines, compensates and functions reasonably well whereas the superagers continue to have the brain function of younger age groups. This separation between bio-age and chronological age can also be seen in the reverse in individuals who seem to languish before their time; those whose genes express disease despite efforts at prevention or who lack sufficient resources to thrive.

Depression is one marker of aging which is most concerning to clinicians which can have genetic repercussions. Recent work suggests that adult experiences of depression can rearrange epigenetic markers in the brain and thereby change our behavior. Several groups of scientists have mimicked human depression in mice by pitting the animals against each other. If a mouse loses a series of fights against dominant rivals, its personality shifts. It shies away from contact with other mice and moves around less. When the mice were given access to a machine that lets them administer cocaine to themselves, the defeated mice take more. Extended hypothetically to humans, the experience of repeated insult, loss,or failure would serve to isolate an individual from society and de-motivate them. Aging on a temporal axis provides a greater probability for insult(s).Again, depression may be an epigenetic disease process which puts the aging at greatest risk.

Another system vulnerable to time is the vascular system. Fortunately, cardiology addresses many of these problems of aging through efforts at preventative cardiology. This filed has a long history of identifying risk patients, initiating treatment, and reducing the impact of the disease. We can learn from cardiology. We should move, therefore, from a focus on dementia as an event that begins with a diagnosis and consider it instead of possible end-stage of a long pathophysiological process that begins in mid-life with a "brain at risk,' like a heart at risk.Ideally, potential for disease would be identified prior to onset, treatment would then focus on the individual's risk factors and lifestyle in order to prevent onset and slow progression. Current methodology results in the dementia diagnosis far too late to afford robust prevention and remediation. Preventative cardiology has shown the way for this.

It appears that we do need a change in the definition of healthy aging to reflect developmental changes. With age we do degrade and have adjustment problems: Life spent with cognitive impairment is fairly constant with increasing age at around 1.4 years in men and 2.5 in women. Cognitive decline is normative. Education, one of those epigenetic change agents, may reduce this by 13% for men and 22% for women. We are of course highlighting an age x environment interaction. The most susceptible functions include gait, IADL, ADL, followed by depression, grip strength, cognition, and others. These also show a downward trajectory as a function of the person and their interactions. Behavioral interventions have shown an effect on longevity such as yoga, internet, being able to hear, as well as all the markers related to exercise and healthy living. Even climate seems to have a major impact on length and quality of life. We have known for some time that CNS disabilities exist world-wide including atrophy, small vessel disease, and infarcts. These too are present as a direct result of the person-environment interface.

Factors which influence epigenetics involve the usual culprits: cognition (subjective memory impairment, mild cognitive impairment, and dementia), affect-based problems (depression, anxiety and somatic issues), genetics (chiefly ApoE-4 allele), lifestyle (diet, exercise, sleep, stress), biomarkers (WMH, tau, Abeta, brain weight), as well as health indicators (morbidities and vascular system). The APOE genotype alone accounts for the clear majority of AD genetic risk (Raber, et al., 2004). The finding of a relationship between AD and APOE genotype has been widely replicated. Possession of one APOEε4 allele increases the risk of developing AD by 3 to 5-fold, and possession of two APOEε4 alleles increases risk by 15 to 20-fold. Regardless, epigenetic changes are a clear marker of aging. DNA methylation-

based biomarkers, often referred to as the epigenetic clock, have been shown to be robust measures of biological age. Epigenetic measures combined with blood cell metrics demonstrate significant association with mortality and promise for predictive ability (Murabito, et al., 2018).

Biopsychosocial Model

The biopsychosocial model is a broad view of health that attributes disease causation or disease outcome to an interaction of biological factors (genetic, biochemical,etc.), psychological factors (mood, personality, behavior, *etc*), and social factors (cultural, familial, socioeconomic, medical, etc.). This model is contrary to the medical model, which is monothetic in its attribution of disease processes. The biopsychosocial model is widely applicable in medicine and social sciences, though its uptake varies across disciplines and cultures. Engel, its progenitor, described the biopsychosocial model as commonsense observation that nature is a hierarchically arranged continuum with more complex, larger units superordinate on the less complex smaller units.

With its roots in social cognitive theory, the biopsycho social model of health implies that treatment of disease process requires the health care team address biological, psychological, and social influences upon a patient's functioning. An individual's social/cultural influences, beliefs about themselves and the world, and genetic predisposition play a part in disease onset and progression. Each of these factors function interdependently and serve to motivate patients towards or away from health promoting behaviors (e.g. smoking, exercise, diet, healthcare access, etc.). Psychosocial factors can cause a biological effect by predisposing the patient to risk factors. For example, depression may not cause poor health on its own. Instead, this psychological factor discourages healthy behavior and may lead to poorer adjustment and depleted environmental resources. Etiology of disease is easily assessed using thebiopsychosocial model of illnesses/disorders.

Despite this, the model flies in the face of real clinical practice. Drug usage can be used as a proxy. After several years of modest growth, prescription drug spending has risen sharply in 2014 with costly new specialty drugs as a major driver in spending. The Medicare share of the national prescription drug spending rose from 2% in 2004 to 29% in 2014(CMS. gov). Nearly one in four people in the United States taking prescription drugs reports difficulty with affording them. This especially applies to older adults. Many specialty drugs are higher priced in the United States and other developed countries. This problem is compounded by widespread polypharmacy in all areas of health regarding older adults. Most authors have defined polypharmacy as the concomitant use of 5 or more medications and excessive polypharmacy as the concomitant use of 9 or more medications. According to Delafuente (2003), the probability of an older adult who takes 5 medications of having an adverse drug interaction is more than 50%, increasing to 100% when 7 medications are taken simultaneously. Older adults with dementia generally receive more medications and are more likely to be taking the potentially inappropriate medications than those without dementia (El-Saifi, et al., 2018).

The biopsychosocial model points out the inadequacy of the current biomedical model in efforts to address diversity in the patient population. As people age, there are more psychosocial factors contributing to their overall health. Mental health accounts for only 6% of all US HC costs but influences 50% of all medical illnesses, indicating a significant imbalance in issues being addressed. Medications for psychiatric drugs exceed all other mental health costs indicating an underuse of non-pharmaceutical therapeutic approaches. Clearly, the biological focus that has accompanied the medicalization of mental health is premature, given the primitive state of our psychiatric scientists. There are deficiencies in the logic and evidence base that supports efficacy claims in both psychiatric drug treatment and the specific empirically supported psychosocial treatments targeted as putatively discrete disorders described in the diagnostic manuals (Woolfolk, 2015).

Functional capacity, or how able a person is to carry out the daily activities of their life, also significantly impacts this population. Activities of daily living (ADLs) decline dramatically between 65 and 74 years - a fourfold change. In the same age span, IADLs declined by threefold. Adults older than 75 years account for 59% of fall-related deaths but make up only 5% of the population. In a review in 2001, Hanlon et al. emphasized the link between the number of prescription medications a female takes and diminished physical and instrumental activities of daily living. The pharmaceutical industry reveals

that 90% over 65 take medications. The number of medications an individual takes concomitantly can have a dramatic effect on health. Older adults with no chronic conditions filled on average 10.9 prescriptions per year. With one or two chronic conditions, the number increases to 24.6. With three to four chronic conditions, it goes up to 44 prescriptions per year. If an older adult has five or more chronic conditions, the average is 60.6. According to the death certificate created between 1969 and 2013, an overall decrease in trend in age standardized death rate was observed for all causes combined, heart disease, cancer, stroke, unintentional injuries, and diabetes, where the rate of decrease appeared to have slowed for heart disease, stroke, and diabetes. It appears this effort at medicating is at least having an impact on length of life, though quality of life is another factor to consider.

As noted previously, a balance of positive and negative genetic factors affect the brain in early/middle life to determine the degree of cognitive agility or impairment at late life. These factors increase or decrease oxidative stress, inflammation, insulin signaling components, size and frequency of infarcts, and concentration of growth factors, cortisol, and other hormones. It is also reasonably true that the mean cognitive decline over 10 years is initiated at several (putatively 7) years before dementia was diagnosed. During these years global cognitive decline measure will lower slowly at first and then pick up speed before diagnosis.

Cognitive decline in AD is nonlinear and precedes dementia onset is established (Wilson, et al., 2012). In fact, disability in old age takes form in a biopsychosocial environment. The death rate for WHO Ministerial Conference on Global Action Against Dementia hosted in March of 2015 showed that the focus on finding causes and cures for dementia, including AD, is intensifying since development of a cure for dementia by 2025 was noted. This but now appears to be highly unlikely. Therefore, risk reduction is the most effective approach to delay onset and potentially reduce new cases. While cognitive decline is a central part (Rajan et al., 2013), the broad spectrum of care mandates that the biological meet the psychological and social factors in the clinical arena.

In the past century, the skill set necessary to practice medicine has changed considerably. No longer are patients dying from infectious disease at the same rate;patients are dying of chronic diseases which progress slowly and lend themselves to psychosocial intervention due to the behavioral component of disease progression. This is where the biopsychosocial model has strong applicability: in later life as the physical and emotional insults accumulate. If one wants to understand the causes and contributing factors of biological diseases, we need to assess the psychological and social factors. Biological disease develops over time if given the appropriate environment for grown, which may include: genetic predisposition, behavioral patterns, and environmental factors, all of which promote or prevent disease development. The biopsychosocial model further assumes there are varying levels of physical, cognitive, emotional, behavioral and environmental factors that contribute to the clinical assessment and conceptualization of the case (Andrasik, Goodie, & Peterson, 2015). Belar and Deardorff (2015) provide clinical goals for working with patients in a healthcare setting which should address questions about the etiology of health and disease that is related to the problem: in the context of biological, cognitive affective, social factors, including consideration of how these factors interact and how these factors influence the choice of empirically supported assessment and treatment.

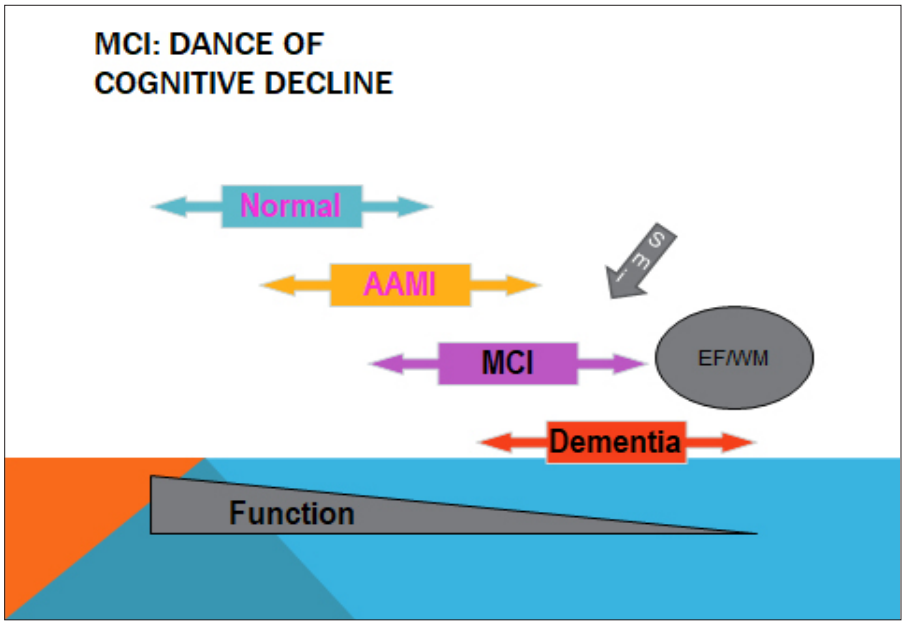
The New Cognitive Aging: Classification and Definition?

Cognitive aging is a gradual, developmental event experienced to a degree by most humans who reach old age. Cognitive aging can be objective assessed thru psychometrics, though it is difficult to define and even more challenging to accurately and reliably measure. Individual differences in cognitive aging may be associated with three broad factors. First are normative, age-graded factors both biologically and culturally determined: developmental milestones of sorts. The second factor includes individual differences in cognitive aging which may also be associated with history-graded events: medical advances and treatment of chronic diseases affecting cognition, economic events, and outcomes of war. Finally, there are non-normative or idiosyncratic life events that affect cognitive aging: individual experiences such as medical events, trauma, or the availability of clinical trials, for example.

Demonstrating this point, age, as a biological factor, is linked to smaller regional brain volumes and poor cognitive performance, including episodic memory. Moreover, neural, behavioral, and cognitive factors completely mediate age differences in episodic memory. Thus, there not only exist multiple paths of influence mediating age effects on memory, but

structural brain measures are central in cognitive aging. There are then multiple dissociations among specific age-sensitive cognitive skills and their reported neural anatomical substrates that support the view that age-related cognitive declines are unlikely to stem from a single aspect of brain aging and are consistent (Marchantet al. 2013).

Due to complex nature of cognitive aging and its influence from multiple factors, it has become even more essential to conceptualize and define the space between normal aging and dementia, termed mild Neurocognitive Decline (mNCD) and formerly known as mild cognitive impairment (MCI). Widely published, the figure below attempts to demonstrate, visually, the decline process. Despite the organization of the figure, this decline process, though fairly regular, is rarely smooth with much variation in progression, severity, and functional loss. Often people iterate between the various types (normal, Age Associated Memory Impairment (AAMI), SCI, MCI and dementia). In normal aging, cognitive decline occurs mostly in speed of processing, working memory, long term memory, information processing (elaborative processing and effortful tasks are poor), source memory, senses (visual and verbal), dedifferentiation (less neural specificity), as well as most fluid intelligence areas. The verbal domains remain largely intact. As problems develop cognitively, MCI has been proffered as a key marker in the decline of older adults. However, what MCI is and how it is measured is much at issue. SCI is the new boy on the block.



AAMI is age associated memory impairment; MCI is mild cognitive impairment;SMI is subjective memory impairment; EF is executive function; WM is working memory

SCI

In 2012, memory joinded the parade of "pre" markers as in diabetes and hypertension and others. The Subjective Cognitive Decline Initiative, SCD-I, working group was formed in response to the challenge to understand the complex and evolving construct of SCD itself. SCD applies to the period of perceived cognitive decline prior to abnormal presentation on standardized neuropsychometric and other clinical measures with retained normal function in IADLs. The heterogeneity of presentation makes prediction of decline during this stage quite complex. The terminology of SCI also is varied; subjective cognitive impairment (Reisberg and Gauthier, 2008), subjective memory impairment (Jessen et al., 2010), and cognitive complaints (Saykin et al., 2006). Regardless, this construct has caught on and has a more data behind it.

SCI

Edmonds and Colleagues (2015) discuss the concept of subtle cognitive decline defined in actuarial terms on neuropsychometric tests performance. They define subtle cognitive decline as: impaired scores (greater than one standard deviation below age-corrected norms), on two measures in different cognitive domains, with a score of 6-8 on the functional assessment questionnaire (FAQ). They found that this criterion had predictive value in determining who would decline to MCI and AD using data from the Alzheimer's Neuroimaging Disease Initiative (ADNI) in that it provides an operational definition of subtle cognitive decline referenced in the National Institute of Aging – Alzheimer's Association (NIA-AA), criterion on preclinical AD (Sperling et al., 2011). Jessen and Colleagues (2013) examined the data from the Age – CoDe Study, a general practice registry-based longitudinal study in older adults, designed to identify predictors of cognitive decline and dementia. Among the individuals with subjective memory impairment and early mild cognitive impairment, risk was assumingly elevated in subgroups of participants who reported concern. This suggests that early in the trajectory of decline, perceived concern has additional prognostic value over and above self-reported cognitive complaints, the presence of which may elevate the risk for subsequent decline to AD and other dementias.

At the individual client level, there are still no reliable objective measures to corroborate a diagnosis of SCD and differentiate it from normal aging. This then places a considerable emphasis on self-report. Of interest it appears that SCD with worry is rather consistently reported over time and is associated with greater increased risk of AD (Wolfsgruber et al., 2016). Such findings indicate that concern or worry about decline has incremental predictive validity over report of complaints per se. Other psychological issues also contribute to psychological factors that influence SCD. Depression elevates the risk of all-cause dementia. Anxiety does the same thing. Worry specifically about cognitive decline is also a potential indicator of SCD and should not be dismissed as evidence of the worried well. There is also accumulating evidence that neuroticism and lack of conscientiousness, in particular, present concerns that lead to risk for MCI and dementia (Duberstein et al., 2011). Physical health, of course, always is an issue in these cases.

In total, clinical assessment of cognitive complaints is still poorly operationalized. Recent qualitative research suggests that certain phenomenological complaint themes may have some specificity for prodromal AD. Miebach et al. (2018) assessed that issue. In a cross-sectional case control study using a mixed-methods approach, 23 memory clinic patients and 21 psychiatric patients with MDD and 21 health controls, age 55-86, were assessed. A newly developed semi-structured interview assessing 12 complaint themes was used, and transcribed open format responses were coded by qualitative expert rating and compared between the groups. Results revealed seven complaint themes, for example, sense of predomination and progression of problems, were significantly more often endorsed by the cognitive complaint groups, together with a novel theme of distractible speech. Complaint themes in those with depression aligned with the depressive symptoms and appeared to be different from the complaint pattern of the cognitive complaint patients. Specifically, themes emerge as being typically depressive. These involve more attentional fluctuation and affect influence on memory, as well as a relative absence of contextualization. SCD then seems to interact with the presentation of their problem state.

MCI

At some point in the decline process MCI enters. It differs from normal aging and is classified as either amnestic MCI (aMCI) and non-amnestic MCI (non-aMCI), and the neuropathology is largely consistent with AD (low A-beta, high CSF tau, atrophy of hippo campus). The progression from MCI to dementia continues at a rough rate of 10-15% per year conversion. The DSM reminds us also that there are mostly preserved functional abilities and there is no extant dementia (>1SD low). Mungas, Brooks, Lowenstein, and Bondi (see Hyer, 2014) are among the many researchers who have noted significant differences in the conversion to a dementia depending on criteria used to define MCI, highlighting the importance of clearer classification criteria.

In an effort to clarify, researchers compare these classification to their nearest relative. The older generation of MCI is dementia and the progression from MCI to dementia depends on the number of

memory or cognitive problems as well as other factors, like poor education, Apo-E4 and others. The younger generation is subjective memory impairment (SMI), which is just "below" normal aging and largely congruent with AAMI noted above. This relative classification may fit well considering that recent studies have suggested that SMI is a prodrome and predictive factor for MCI and dementia, especially when comorbid with a depression or sleep problems. Mewton et al. (2014) looked at over 1900 community dwelling participants between 65 and 85 and measured subjective memory complaints. Of those who reported subjective memory problems (35%) also reported issues of psychological distress (especially in the last 5 years), poor functioning, increase health service use, and negative self-assessed mental and physical health. This occurred in people with MMSE >27. Does this correlation between perception and predictive ability indicate insight ahead of time or epigenetic influence?

Also concerning MCI, there are no FDA approved treatments (Petersen et al. 2001). Many actually can revert back to the normal range without treatment, though most do not change status. Regardless, clinical interest for MCI is an exciting and fortuitous "problem." By using this designation clinicians argue for continued hope, challenging and healthful lifestyle growth, and the monitoring of tasks most of concern to older adults fearful of dementia -- Driving (40%), Work (12%), Relocation (31%), Firearms (50%), Being treated differently (40%), Social limitations (31%), and Needing care (50%). In other words, as this classification of cognitive decline becomes more concretely defined, interventions and treatments will follow. The ambiguity present now leaves much room for improvement. In fact, MCI highlights at least two decades that have seen an increased respect for the continua theories of pathology which notes the variants of subclinical health problems. We just need to identify the best markers of risk, watch these risk factors, and then at some point treat: a watch and wait approach.

This table presents the issues in prediction of progression from normalcy to subjective mental impairment and eventually MCI and dementia. In meta-analyses, episodic memory scores are still significantly more predictive in detecting preclinical AD than CSF biomarkers (Schmand et al., 2010).

- Problem is the abnormal processing of B-amyloid peptide → plaques
- This process occurs while person is still cognitively normal
- Biomarkers of B-amyloid are reductions in CSF AB42 and increased amyloid PET tracer retention.
- After a lag, neuronal dysfunction and neurodegeneration become the dominant biomarkers.
- Biomarkers of neuronal injury and neurodegeneration are increased in CSF tau and structural MRI measures of cerebral atrophy.
- Cognition falters: Neurodegeneration is accompanied by episodic memory problems along with synaptic dysfunction which is marker by uptake on PET.

Despite the lack of clarity in how to define decline, accurate and empirically supported assessment of cognitive function leads to more reliable diagnoses and more reliable associations to biomarker outcomes and rates of decline. This improved reliability helps provide patients and families with useful information and practical recommendations. While earlier diagnosis would improve outcomes, it is difficult to accomplish due to the variability in presentation of patients and baseline factors such as intellectual function. In one study, Rentz et al. (2004) discussed the use of IQ adjustment norms to predict progressive decline in older adults with above-average intelligence as an attempt to detect decline earlier. This was successful. In this same vein, Jak et al. (2009) identified four clusters that emerged in preclinical work prior to AD diagnosis. These included dysexecutive problems, amnestic MCI, mixed MCI, and a group that had a single impaired test score on the measure of visual spatial function. He prudently insisted that two measures be applied for a determination to be made of any of these forms of MCI. These efforts are making incremental movement towards better classification of cognitive function or decline.

Cognitive Reserve

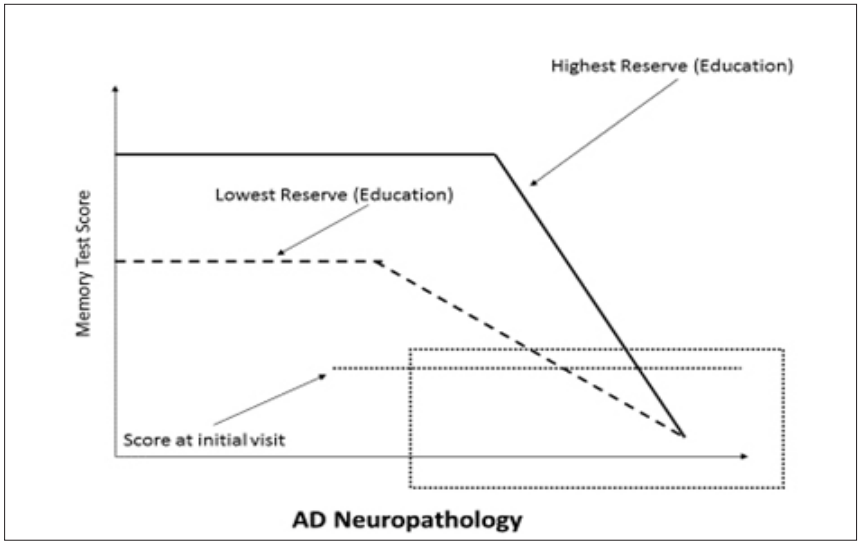
MCI and its variability imply the concept of reserve, cognitive or brain. In the neurodegenerative process the person with reserve has an assist during the early stages of neurodegeneration; symptoms arise later in

the process, if at all. After a period of time, the level of symptoms catches up and the person shows a more precipitous trajectory of decline; in fact, cognitive reserve patients have more impaired brains (metabolic and perfusion deficits). The idea of reserve against brain damage stems from the repeated observation that there does not appear to be a direct relationship between the degree of brain pathology or brain damage and the clinical manifestation of that damage. Some time ago Katzman et al. (1989) described 10 cases of cognitively normal elders who were discovered to have advanced AD pathology in their brains at death. They speculated these subjects (all women) did not express the clinical features of AD because their brains were larger than average. Similarly, most clinicians are aware that a stroke of a given magnitude can produce profound impairment in one patient, while having minimal effect on another. Something must account for the disjunction between the degree of brain damage and its outcome. The concept of reserve has been proposed to serve this purpose.

One convenient, although not entirely accurate, subdivision of reserve models revolves around whether reserve is a passive process, or the brain is actively attempting to cope with or compensate for pathology. In passive models, reserve is defined in terms of the amount of damage that can be sustained before reaching a threshold for clinical expression. In the active models, reserve revolves around differences in how the task is processed. These two approaches are not mutually exclusive. Ultimately, some combination of these two approaches might best describe the empirical observations that have prompted the development of the concept of reserve.

One of the key outcomes in the study of reserve is the presence or absence of some clinical entity. For example in AD, many studies have attempted to determine whether there is a relation between some measure of reserve, such as education, and the prevalence or incidence of AD. Many studies have observed higher prevalence of AD in individuals with lower education. Note that the assumption here is that since education is associated with reserve against the expression of AD pathology, AD should be less prevalent in individuals with higher education. These studies most often contaminate this conclusion by not directly measuring AD pathology, and thereby assuming that its prevalence is relatively equal across education groups.

Cognitive reserve is, however, a rich concept that has heuristic value for clinical work. While reserve is basically a simple concept, upon consideration there can be many layers of theoretical complexity. Consideration of the concept of reserve suggests that it cannot be considered as a unidimensional entity. Brain reserve and cognitive reserve produce different predictions about the impact of brain pathology on function. Further, the differentiation of reserve and compensation may have practical utility particularly when applying functional imaging. Below we can see the trajectories of a low and high reserve person. While this figure posits that both low and high reserve show a similar score at one point in time (e.g., MMSE =17), clearly they are different people and have different clinical profiles.



Cognitive Reserve and Scaffold Theory

One model that accounts for the taxonomy of cognitive aging and reserve is the scaffold theory (Reuter-Lorenz & Park, 2011). Reuter-Lorenz and Park have established a conceptual model of a scaffolding theory of aging and cognition which shows that older adults may achieve preserved cognition by means of preserved neurobiology or compensatory processes or some combination of these factors. It is a hallmark of successful cognitive aging if one is able to maintain abilities and underlying neurobiology. This results in assessment requiring longitudinal measures to evaluate the degree of change over time. Neural resource enrichment in this model includes such things as cardiovascular fitness, education, as well as brain reserve, while neural depletion includes such things as ApoE4 or vascular risk factors, heart disease, stress, among other problem areas.

This model provides us with a good understanding of the problems of compensation and cognitive reserve. A balance of positive and negative genetic and environmental factors affect the brain in early/middle life to determine the degree of cognitive agility or impairment at late life. These factors increase or decrease brain factors, oxidative stress, inflammation, insulin signaling components, size and frequency of infarcts, and concentration of growth factors, cortisol, and other hormones. Scaffolding or secondary networks are an important part of normal aging. This allows for the maintenance of cognitive functioning as age associated structural deterioration occurs. This process is very efficient in youth and stands at the ready at late life. With age the scaffolding process may be invoked to perform familiar tasks as done in youth as these processes become increasingly more challenging. Extrinsically, the brain is confronted with novel or increased demands; intrinsically biological aging asserts itself. At some point scaffolding will meet its limit due to pathology as in AD. The pathology increases and the reparative processes wither.

The idea then is that, despite pathology, older adults compensate by scaffolding. This is the recruitment of additional circuitry that shores up declining structures whose functioning is noisy. Over-activation of the prefrontal sites accompanies the under-activation of the posterior sites of occipital and parietal lobes. Generally, this involves bi-lateral activation. Both hemispheres are involved. Scaffolding is then not a sign of pathology; rather it is compensatory in design and nature. It has strengths; physical fitness, cognitive stimulation, occupational attainment, education.

Cerebral-Vascular Health

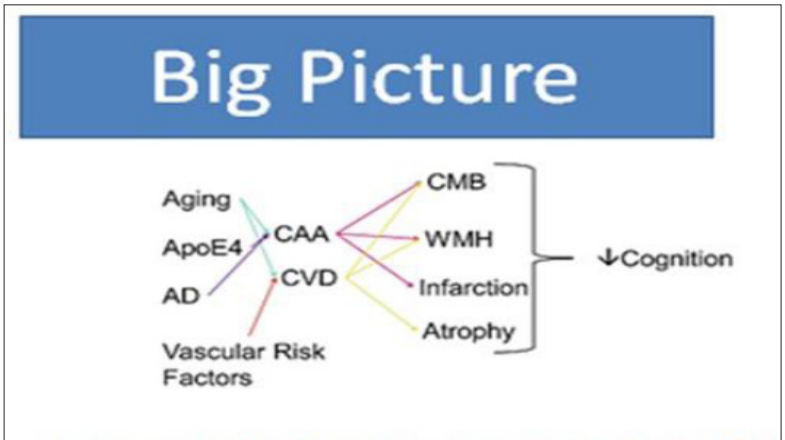
Cardiology as a profession has had many decades to improve upon their treatment methods. Vascular health is critical for physical health and has received its due attention as a life sustaining function. Its role in cognitive health has received less attention despite its commensurate importance. Brain aging needs a readjustment like that of chronological aging. As noted before, normal brain aging accounts for changes that occur over time and assumes a process of slow degeneration without impairment in function relative to same aged peers. Clinically silent brain infarcts increase over the life span at a 75% rate. This includes cerebral microbleeds, small dot-like lesions with low signal intensity which accumulatively can be quite troublesome. Ten percent of community older adults (50% in stroke patients) have this. Even minor cognitive declines can measurably influence clinical outcomes like rates of hospitalization and medication adherence (El-Saifi, et al., 2018). By contrast, healthy brain aging involves maintained systems which do not degenerate and is much less common in the general population. These may be the aforementioned "superagers."

Cerebral small vessel disease (CSVD), the entity responsible for the pathogenesis of ischemic strokes, cerebral hemorrhages, and encephalopathy, is the pathological process of subcortical structures, such as lacunar infarcts, white matter lesions, and micro-bleeds. Its predecessors are chronic diseases as hypertension and diabetes mellitus. CSVD mainly consists of a lacunar infarct or lacunar stroke, leukoaraiosis, Binswanger's disease, and/or cerebral micro-bleeds. With the development of imaging examination and its clinical usage, it has been determined that cerebrovascular disease, especially CSVD, contributes to the occurrence of AD. CSVD is responsible for 20-30% of the cases of ischemic strokes, as well as for a considerable portion of the cerebral hemorrhages and encephalopathy. CSVD gradually develops into a decline of cognition, vascular dementia, and impairment of gait and balance, mood,

depression, urinary incontinence, and often results in greater social and economic burdens (Cai et al., 2015). Gait slowing and cognitive decline are both common in older people. In addition, high fatigability, IL-6 dysfunction, other pro-inflammatory state, and executive dysfunction are also sequelae (Lin et al., 2014). Perhaps the most common contaminate of a degenerative process is the cardiovascular system.

Cardiology has become notably adept at treating human vasculature, but it remains unclear whether effective treatment of vascular risk factors prevents cognitive decline and clinically silent brain injury and whether antihypertensive treatment really reduces incident dementia (Jongstra, Harrison, Quinn, & Richard, 2015). The appropriate watch and wait window also remains unclear; should any waiting occur at all? It is even unclear whether some individuals are at risk and need to be treated differently (family history, genetic markers) or how the time course of vascular brain injury relates to neurodegenerative brain injury.

We do know that synaptic density is the most accurate biophysical correlate of cognitive impairment with hippocampal atrophy also quite analogous. Cardiovascular health, however, contributes to this generative ability and subsequent cognitive health. As represented in the graphic below, aging, genetics, AD, and poor vascular function lead to cerebral amyloid atrophy and cerebral vascular atrophy leading to micro-brain bleeds, white matter hyperintensities, infarcts, and brain trophy (Lockhart & DeCarli, 2014). This results in reduced cognitive ability. Neuropsychologically we will see executive function, attention, and processing speed especially suffer. Affectively, depression is a marker as reflector and a consequence of cognitive problems (Wong, et al., 2016). Behaviorally, disinhibition and less ability to tolerate discomfort and handle stress results in unhealthy choices. Health-wise, this aspect of living is always relevant and important.



Graphic summary of the multi-factorial relationships between age, genetics, vascular risk factors, and Alzheimer's disease that results in cerebral amyloid angiopathy (CAA) or cerebrovascular disease (CVD) that lead to cerebral microbleeds (CMB), white matter hyperintensities (WMH), infarction and brain atrophy all of which contribute to reduced cognitive ability (Lockhart, S., & DeCarli, C., 2014).

It is clear now that vascular problems set the stage for AD decline. In fact, the presence of vascular problems allows the presence of AD to present sooner and more virulently. This especially is a problem with the presence of amyloid. So, the contamination of vascular pathology appears to be both co-incident with AD. It requires a healthy lifestyle to prevent this.

Lifestyle

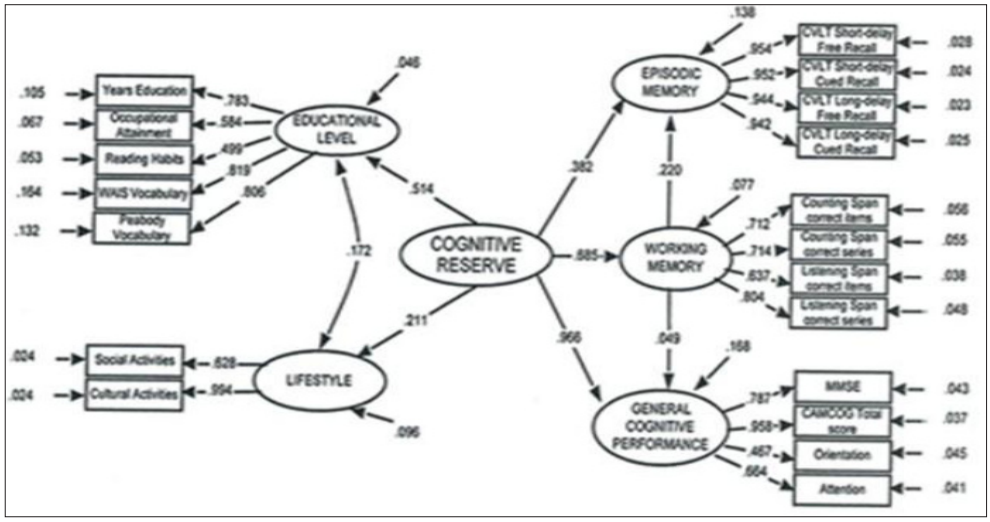
In this paper, lifestyle is a behaviorally modifiable element in treatment of chronic disease: how we choose to live. True health requires healthy behavior. Luck rarely keeps people healthy. Life value and health in general rest on our daily behavioral routines. DeVol and Bedroussian established in 2007 that five behavioral factors contribute to 70% of morbidity and mortality: diet (what *and* how much), physical exercise, smoking, and alcohol consumption. Sleeping, mating, drug use and relationship habits account for another significant proportion of the burden of chronic and infectious diseases (Chorpita, Miranda, & Bernstein, 2011). Similarly addressing dementia, Gatz et al. (2005) using a longitudinal view of the Swedish Twin Registry looking at a sample of nearly 12,000 twins now over 65 found that diabetes and obesity are among the most significant NON-genetic risk factors for AD and dementia. Barnes and Yaffe (2011) proclaimed the need to focus future efforts on

addressing potentially modifiable risk factors. A sedentary lifestyle leaves older adults at risk for just about everything. The common theme among these risk factors is our ability as humans to impact them through behavioral change.

Cognitive Reserve and Training

When one addresses lifestyle, the construct cognitive reserve again emerges. As noted above, MCI is such a cognitive marker. Cognitive reserve has been explained as life in the context of cognitive decline, when the brain attempts to compensate for aging (Reuter-Lorenz & Park, 2011; Cheng, 2014). Cognitive decline, in effect, triggers the use of reserve capabilities which mask cortical changes until a certain threshold is reached. At this point, dementia is manifested along with the more accelerated downhill course. Lifestyle habits make a difference. Cheng espouses cognitive reserve as the marker to alter the clinical trajectory in several ways. Those with higher cognitive reserve are expected to show delay of the MCI traits as they are more able to tolerate insult to the brain. Increasing evidence suggested intellectual activity, as well as physical activity, is very congruent with the model of cognitive reserve.

Lojo-Seoane et al. (2014) presented a model of cognitive reserve based on education level and lifestyle. The authors present a structural model that analyzes the effect of cognitive reserve on three cognitive domains: episodic memory, working memory, and general cognitive performance. They developed and analyzed a structural equation model to study cognitive reserve and cognitive performance in 326 participants over 50 years of age with subjective memory complaints. The cognitive reserve construct was found to consist of two factors: An educational factor and a lifestyle factor. The model revealed that cognitive reserve had significant direct effects on episodic memory, working memory, and general cognitive performance and indirect effects on episodic memory via working memory. This model has become necessary as studying validity of a cognitive reserve construct and its relation to cognitive function has increased in recent years with supportive divergent and discriminative validity. This model (see below) clearly highlights the significant impact of education and lifestyle on cognitive reserve.



An additional effort at discovering the mechanisms of cognitive reserve, The MIDUS study demonstrated that a composite index of a number of adaptive psychosocial and behavioral factors was positively related to cognitive performance and change over and above the role of physical factors, health factors, and cognitive activities. Whereas previous studies have examined these factors individually, Agrigoroaei and Lachman (2011) showed that the accumulative association and protective value for cognitive functioning of these variables. Interestingly, the effects of the protective factors were equally beneficial across adults within old age. Another key promising finding was that education differences and episodic memory and declined reasoning abilities were significantly attenuated as a function of a number of protective factors. People who engage in frequent cognitive activity can compensate for education differences. Cognitive factors over time, as well as non-cognitive protective factors, make a difference. This suggests that the cognitive risks traditionally associated with low education can be attenuated by modifying a large spectrum of lifestyle factors.

It is not entirely clear whether cognitive training (CT) activities at the MCI stage should simply be a continuation of previous activities from specific efforts of resuscitating cognitive reserve. A multidimensional approach to rehabilitation, CT, allows treatment to address cognitive or functional abilities with the goal of enhancing impaired abilities (cognitive remediation) or maintaining intact abilities and preventing decline (cognitive training). There are many empirically supported cognitive rehabilitation strategies involving rehearsal based and internal compensatory strategies which address each skill level and potential outcome (Hampstead, Briceno, & Garcia, 2018).

The most cited and relevant study in cognitive training is the ACTIVE trial, due to the unprecedented longitudinal nature of data collection. Three conditions (memory, reasoning, and speed of processing) maintained their training effects on the ability at 5-year follow-up compared with the no-treatment comparison group. This was so for both a booster group and a non-booster group. At 20 years follow-up, the speed and reasoning group maintained their training effects on the ability trained, compared with the no-treatment control (Willis, 2018). The initial training included only ten 75-miniue sessions. Booster sessions were available 1 and 3 years later. Also, the ACTIVE 10-year retention rate was 44%. These were cognitively normal subjects. Unverzagt et al (2007) did identify a memory-reduced group (probable MCI). This group did not benefit from the memory training but did so from speed and reasoning. CT did not appear to prevent cognitive decline, as five years post training the more impaired group as a whole did not have a reduced prevalence of dementia. Again, this was an undefined impaired group.

There is little direct evidence on cognitive-intervention - based studies showing risk reduction in dementia, most severely impaired older adults. There is also limited evidence that cognitive training gains in healthy patients translate to the real world, which is encouraging new efforts at discovering the mechanisms underlying gains in cognitive training (Wolfe, et al., 2018). Despite this, The National Institutes of Health Consensus Development Conference Statement on Preventing Alzheimer's Disease and Cognitive Decline (Daviglus et al., 2010) suggested that, "increased involvement in cognitive activities in later life may be associated with slower cognitive decline and lower risk for mild cognitive impairment" (p.10). Implied is that individuals should take actions that promote cognitive health, including engaging in lifelong learning. Without knowing the exact mechanism, recommendations can be made which support health, giving individuals the opportunity to engage in activities which promote social and psychological function in addition to a physical component (like attending a cognitive training group).

One last word about the construct of CT and rehabilitation, through a lens of psychology and aging. It is a messy construct that is an over-arching philosophical approach to treatment. Rehabilitation is a more patient-centered collaborative process that is multi-modal, holistic, ecologically relevant, and always situated within the person's own goals. The holistic approach follows the approach of other clinician researchers in both acquired brain injury (Cicerone et al., 2008) and in older adulthood (Huckans et al., 2013). It sets person-specific goals and measures the person on these individual targets (goal attainment scaling). Impaired older adults often improve but it is very specific and often not transferable. This also means being transparent at every step of the process about how the problem is being conceptualized, what the recommended course of intervention is, and how the intervention is expected to impact on a client's everyday function (Tuokko and Smart, 2018).

Cognitive Improvement Concepts

Cognitive training itself involves a guided practice-set of standard tasks designed to impact specific cognitive functions with a range of difficult levels.

Cognitive stimulation is typically applied to persons with diagnosed dementia. It is a simpler task and involves reality orientation and the like.

Cognitive rehabilitation has a greater focus on individual needs and goals of the client. What might be broadly considered cognitive rehabilitation, in fact, is a blend of restorative activities.

Exercise

Exercise helps everyone and in ways related to adjustment and cognition and increasingly biomarkers. The World Health Organization (WHO) has argued for an active aging framework which encourages mental activities as well. The Alzheimer's Association notes a consistent and strong correlation between declines in ADL function, which requires physical and intellectual effort, and cognitive ability when a medical diagnosis does not explain the decline (Cordell, et al., 2013). However, unlike physical activities, there have been no established mechanisms or organized attempts to promote intellectual activities at the population level.

There may be a need to bring cognitive health into the policy agendas alongside the traditional focus of physical health and to issue guidelines on this practice. In this population it is important to note that, the presence of cognitive impairment, as well as declining vitality and physical health may themselves constitute a barrier to this participation. This is another reason why we espouse using a Watch and Waitmodel, as it allows for intervention as these barriers present themselves.

Intellectual and cognitive exercise is crucially protective, while physical exercise shows promise in reversing decline. Randomized studiesof MCI patients are now demonstrating that vigorous physical exercise not only improves cognition, but also moves AD biomarkers in the right direction. In one study by Baker (2015), phosphorylated tau, a marker of neuronal injury, fell significantly in the cerebral spinal fluid after six months of aerobic exercise. Ranging from age 55-89 (n=71), participants who were previously diagnosed with MCI and pre-diabetes were randomized to either a controlled program of stretching three times a week or an exercise program of aerobic exercise for 45-60 minutes per week. There were no reductions in CSF tau in the groups with stretching. However, the exercise group experienced significant declines in CSF tau.

Value of Exercise

Frequently, new data suggests that physical activity not only improves executive function and cerebral blood flow but may also reduce amyloid and tau levels in the brain. Recently findings were presented here at Alzheimer's Association International Conference (AAIC) 2017 supporting the benefits physical activity. Much of the focus of this year's (2018) AAIC meeting was on lifestyle interventions – healthy eating, reduced stress, adequate sleep, and increased physical activity – to help prevent dementia. Some experts believe that of all lifestyle factors, exercise is tops when it comes to preserving cognition.

In recent years, the identification of biomarkers for AD has made it possible to compare levels of amyloid-beta (Aβ) and tau in those who are and those who are not physically active. One new study (Brown et al., 2017) evaluated the relationship between exercise levels and brain amyloid load in carriers of genetic mutations that cause autosomal-dominant AD. The analysis included data from the Dominantly Inherited Alzheimer Network (DIAN) for 139 pre-symptomatic mutation carriers. These patients are destined to develop AD and know approximately when they will start having symptoms. Patients were categorized into those reporting fewer than 150 minutes per week of (low exercise) and those reporting 150 minutes or more per week (high exercise). The researchers also had information on brain amyloid load, as quantified by Pittsburgh compound B positron-emission tomography (PiB PET). They stratified patients in order to investigate those with high brain amyloid levels (PiB+).

Compared to the high-exercise group, the low-exercise group was older (38.6 years vs 33.7 years) and had more depressive symptoms, as measured by the Geriatric Depression Scale (2.2 vs 1.4). When the entire cohort of mutation carriers was examined, there were no differences in amyloid load between patients in the low-exercise group and those in the high-exercise group. However, for the 16 patients with PiB+ in the low-exercise group, the mean level of brain amyloid was higher than in the 55 patients with PiB+ who were in the high-exercise group (P = .007). The researchers were able to show that Aβ in those in the high-exercise group accumulated at a slower rate relative to what would be expected. The results suggest that higher levels of exercise may delay the accumulation of Alzheimer's pathology and subsequent symptom onset in Alzheimer's disease mutation carriers. One big question is, does the lower Aβ mean that onset of symptoms will actually be delayed?

In other research presented at the meeting, Brown's group added to their previous work showing a relationship between physical activity and lower brain Aβ levels. With the recent advent of tau PET tracers, they were able to show that in a group of 88 cognitively healthy older adults, mean cortical tau burden was higher in those reporting low to moderate physical activity than in those reporting a high level of physical activity (P = .02). It is believed that brain amyloid deposition precedes tau accumulation and that density of neurofibrillary tangles (composed of tau) is more closely associated with cognitive impairment and neurodegeneration, significant biomarkers.

Of all lifestyle interventions aimed at preventing dementia, there seems to be more evidence for physical activity, possibly because it more directly affects cerebral blood flow. When you give someone, say, 6 months of exercise, 6 months of moving their legs, you see more effects in their cognitive score than if they did 6 months of CT. The activity does not have to be strenuous. Accumulating evidence suggests that yoga, tai chi, and mindful practices may also be helpful. And some studies have found positive effects from combining strength training with aerobics. Of all the possible lifestyle changes, exercise has been proven to have the biggest impact.

Finally, exercise trumps depression. In jut one study, HUNT study (Nord-Trondelag Health Study), Harvey et al (2018) followed over 33,000 healthy adults in Norway starting around 1985 and following them for at least 11 years. Participants were screened very carefully to ensure that they were healthy, having no pre-existing history of depression. Exercise did not protect against anxiety. However, exercise did have a significant effect on depression. The study investigators estimated that compared with individuals who did not exercise, those who exercised an hour or more a week had a 44% decreased odds ratio of being depressed; quite a significant finding. These researchers also noted that depression was a causal factor, about 12% of cases could be prevented if all adults exercise for a little over an hour a week.

If exercise is so great, why doesn't everyone do it? Phillips and Gardner (2016), asked which behavioral components contributed to consistent exercise, among pre-exercise(instigation) habits and during-exercise (execution) habits. These authors note the reduced cognitive effort in habitual practice; it will be easier if it becomes automatic. They found that instigation habits, meaning cues which produce a behavioral initiation impulse, produce more frequent exercise than execution habits, or the routine-ness of the exercise. The act of initiating exercise should become the routine. A holistic approach allows for developing cues for the individual; behavior that makes the act of exercising feel subconsciously compulsory. From the health perspective, it is important that people engage in physical activity frequently and so an instigation habit is the type of habit to promote to make that happen.

Socialization

In the scope of cognitive aging, socialization is a factor which can promote or deter healthy development. The quality of social interactions, positive or negative, impacts the way we think.Being alone is especially troubling especially after a stressful episode or a loss. Men are at most risk as they are more susceptible to isolation.The World Health Organization (WHO) lists poor social support networks as detrimental to health and the United Kingdom's Ministry of Health established loneliness as a health priority. Social relationships therefore are a critical issue in healthcare. Hertzog et al (2008) revisit longitudinal studies which support the idea that being socially engaged promotes maintenance of cognitive health. Being socially isolated and feeling alone is the functional equivalent of 16 cigarettes/day.

Collected census data provides that 27% of the U.S. population lives alone, over half is unmarried, and 1 in 5 never marry. Another 15-20% have only one friend. The divorce rate in the United States continues to hover around 40% for first marriages. Although caution must be used in suggesting single, widowed, or divorced adults are less socially connected than those who are married, the structural dimensions provide robust indications of health risk. In fact, between 20 and 43% of the U.S. adults over the age of 60 experience frequent or intense loneliness, higher than the prevalence of merely living alone (Perissinotto, Cenzer, and Covinsky, 2012). Taken together with

an aging population, smaller families and greater mobility reduces the ability to draw upon familial resources of informal support in old age. Decreased community involvement is also evidenced by falling rates of volunteerism and an increasing percentage of Americans reporting no religious affiliation. Smith et al. (2018) found social isolation to be a significant risk factor for mortality.

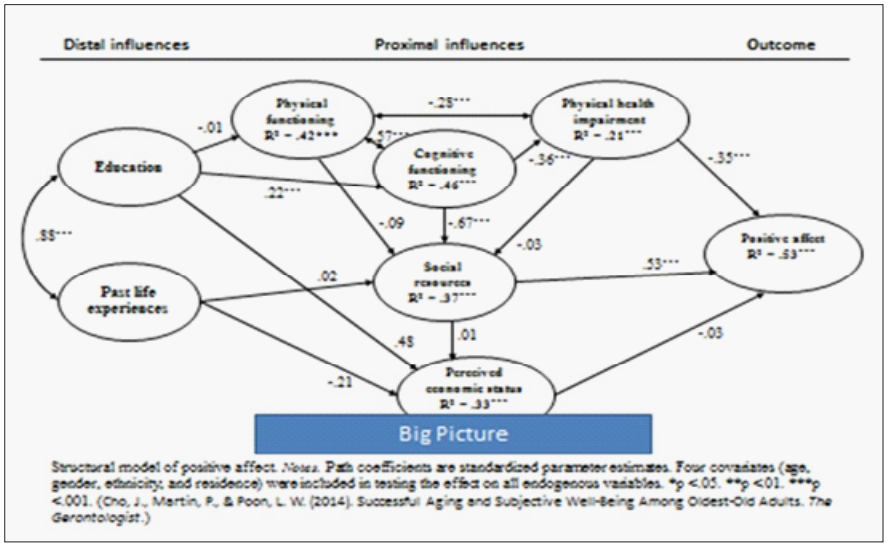
In sum, a significant portion of the U.S. population lacks social connectedness, which places them at greater risk for premature mortality and underlying morbidity and the magnitude of this risk is comparable to that of currently recognizable leading health determinates (Pynnönen, et al., 2012;). Not only is the level of involvement relevant, but also the quality. Data from a national sample of older adults, aged 65 to 91, revealed that those who experience persistently high levels of negative social interactions (for example, support letdowns, rejection by others) over a two-year period reported poor self-health, more health conditions, and greater fundamental impairment (Newsom, Mahan, Rook, and Krause, 2008). Remarkably, one study of individuals 48 to 77 found that the number of ambivalent social ties, but not the number of aversive social ties, and participant social networks was related to shorter telomere length, an indicator of accelerated aging (Uchino et al., 2012).

Physical Health, Stress and Relaxation

Numerous studies represent the fact that the relaxation response in psychophysiological state of deep rest induced by practice, such as mediation, yoga, and prayer, not only relieves feelings of stress and anxiety, but also affects physiological factors, such as blood pressure, heart rate, and oxygen consumption. A study out of the Institute of Technology Assessment and Benson-Henry Institute for Mind/Body Medicine at Mass General Hospital finds that individuals participating in a relaxation-response-focus training program use fewer healthcare services in the year after participation than the preceding year, as much as a 42% decrease in service utilization (Stahl, et al, 2015). The controlled group, on the other hand, had an overall but not statistically significant increase in service utilization in that second year.

The impact of poor mental health on physical health is no longer arguable (see biopsychosocial above). Health, especially mental health, matters. Proctor et al. (2003) studied the interaction of comorbid medical conditions and depression (being used as a marker for overall mental health), which revealed startling results. Hospitalized depressed elderly patients evidence high medical comorbidity with three-fourths having at least one medical illness serious enough to require medical treatment. Vascular, cardiac, musculoskeletal, and neurological conditions are most prevalent, suggesting the need for universal monitoring with larger samples. The rate of heart disease compares with that of older adults hospitalized for reasons other than depression, but the findings of this group indicate a higher than expected frequencies of hypertension, Parkinson's disease, osteoarthritis, COPD, and diabetes among the depressed elderly patients. Subgroup analysis focusing on depression within these most common medical conditions, particularly the vascular conditions, project trouble, with female gender, low SES, greater age, lower MMSE score and presence of depression resulting in even greater probability of reduced functional ability. Depression and cognition would have a direct impact on total functioning, but they would also have an indirect impact on medical comorbidity.

While it is simpler to examine these lifestyle factors in isolation, Cho, Martin, and Poon (2013) developed a "big model", a schema based on the previous Martin and Martin model of aging. Results showed that significant direct effects of physical health impairment and social resources on positive aspects of subjective wellbeing among the older old adults. They also found significant indirect effects of cognitive functioning and education on positive affect among the oldest old adults. Social resources mediated the relationship between cognitive functioning and positive affect and cognitive functioning and social resources mediated the relationship between education and positive affect. In addition, physical health impairment mediated the relationship between cognitive function and positive affect and cognitive function and physical health impairment mediated the relationship between education and positive affect.



Structural model of positive affect. *Notes.* Path coefficients are standardized parameter estimates. Four covariates (age, gender, ethnicity, and residence) were included in testing the effect on all endogenous variables. *p <.05. **p <.01. ***p <.001. (Cho, J., Martin, P., & Poon, L. W. (2014). Successful Aging and Subjective Well-Being Among Oldest-Old Adults. *The Gerontologist*.)

There are other factors that make a difference at later life; dietary changes, dietary supplements, and the "purpose medications," such as those currently used for cholesterol or hypertension, as well as the growing number of investigational disease modifying agents. What one does makes a big difference across the lifespan. Yaffe et al. (2001) noted that the determinants of cognitive aging in men and women; 30% were maintainers, 53% were decliners, and 16% were major decliners. Not surprisingly, problems tend to compound themselves: 68% of adults with mental health conditions also have medical conditions, and 29% of adults with medical conditions have mental health conditions (Clay, 2013).

Stress reduction and the relaxation response make a difference. The relaxation response, mindfulness, controlled breathing and meditation now have considerable merit. The relaxation response can take many forms; meditation, yoga, deep breathing, repetitive prayer and mindfulness. The overall message is the various forms of the relaxation response address the fight-flight response. It reduces the cascade of the SNS and the adrenal medulla that results in hyperarousal. The benefits are many: Self-education, relationships, creativity, play, health, altruism, spirituality, and self-transformation.

Two other forms of the relaxation response are worth noting. Mindfulness is a newer RR. It is paying attention in the moment, on purpose and mindfully. The effort is to bring attention to individual moments in your life without judgment and defense. In a mindful moment the person observes the self at that time including the evaluations you make, sensations you feel; not judging what you are thinking in the moment; be non-judgmental even about your judgments. There is considerable research on its value and efficacy (Segal, 2014). Similarly, the third wave treatment in psychology ACT, Acceptance and Commitment Therapy, espouses a view of life as one of acceptance and commitment Hayes, 2008). ACT assumes suffering is normal. Less emphasis can be placed on problem-solving (i.e., ridding oneself of depression) and greater emphasis on the role of such problems being barriers to living. ACT is the focus should be not on fighting the battle against a psychological problem (i.e. depression), but on lessening the impact of the problem on the life of the individual. The appearance of distressing thoughts and feelings might not change but its impact CAN change.

Prevention

We follow up on lifestyle with prevention from a more societal level. Let us consider depression again, the model for health problems. In 1984, the National Institute of Mental Health Public Information pamphlet entitled "Depression, What We Know" stated in general the onset of clinical depression cannot be prevented (Munoz 2012). However, in 2009 a report, "Preventing Emotional and Behavioral Disorder Among Young People: Progress and Possibilities" listed several random trials, in which the proportion of new cases of major depression was significantly reduced in participants randomly assigned to preventive intervention participation relative to control group. This has directed new resources to the mental health field to prevention research practice and training. At different stages some factors, for example, parental bereavement, divorce, or having serious medical illness, may increase the likelihood

of a child developing difficulties, while others, for example the presence of stable relationships, good schools, effective vigilant parenting, may promote the development of resilience.

Integrative care, using the biopsychosocial model, suggests that causation is determined in part by familial and genetic factors and in part by the current life adversities and emphasized that vulnerabilities may be expressed in different ways at different developmental epics. These results apply in very old people at the subsyndromal level of depression which is prevalent (Ludvigsson, Milberg, Marcusson, & Wressle 2014). The effort, however, is not to simply apply research about young people to the aging, but instead figure out how these results can inform research in the aging population. The life sources of stress are both similar and different between these developmental stages, indicating a need for case-by-case assessment of vulnerabilities and resulting catered interventions.

Primary care is a team sport. Efforts to identify those areas in which physicians have the greatest concerns are a crucial part of recognizing where the greatest challenges and risks in primary care remain. Primary care is the first stop to connect patients—especially those with complex health needs, such as multiple chronic illnesses—with other necessary services, including specialists, after hours or home care, and social services. In a summary from the Commonwealth Fund's 2015 International Health Policy Survey, around 500–2900 physicians from each of ten industrialized countries were surveyed to gauge their perspectives about their preparedness for providing care for patients with complex health needs in the primary care systems in which they work (Osborn et al., 2015). The results show that there is almost universal difficulty in coordinating care for patients with complex health needs. Managing care for patients with mental health issues and substance disorders is a particularly problematic area, with less than 50% of physicians from nearly all the countries surveyed reporting that their practices were prepared for such patients. Interestingly, Canada (49%) and the USA (38%) have the lowest percentage of practices that make after-care arrangements, which is a likely driver in the higher use of emergency departments for chronically ill patients in those countries.

This is, again, a suitable area for behavioral change which promotes longevity and health. Higher education level and literacy consistently predict late life health and disability, lower risk of obesity, later life diseases including Alzheimer's disease and cardiovascular diseases. The effects of unhealthy lifestyles in childhood and adolescence are manifested in young adulthood as atherosclerosis of the arteries, a precursor to cardiovascular disease. Prevention or treatment of hypertension and diabetes at every age is associated with decreased risk of heart disease, stroke, and recurrent events. Individuals with fewer social and economic resources manifest chronic diseases and disability earlier in their lives than those with greater resources and access to healthier lifestyles. In middle adulthood, cognitive enrichment and occupational and other exposures are protective against late life dementia. Cognitive activity in late life can improve cognitive reserve and delay or prevent cognitive decline (Hertzog, et al., 2009). Exercise and appropriate nutrition can increase muscle mass and strength in frail nursing home patients and decrease the incidence of frailty.Interventions which utilize yoga practices improve balance and mobility in the elderly (Youkhana, 2016).

There is strong evidence that primary, secondary, and tertiary prevention are effective in preserving or improving health and function in older adults. Notably, both primary and secondary prevention of non-communicable diseases, especially hypertension, smoking, obesity, diabetes, cardiovascular diseases, and selective cancers implemented after age 50 and after age 65 are highly effective, as are interventions to prevent other geriatric conditions, such as falls. In addition, stroke prevention has shown good potential for also preventing cognitive decline and dementia. Treatment takes place largely in a primary care clinic. Physicians are the gatekeepers. But a rising number of patients at risk for chronic diseases, an aging population, and life-prolonging medical interventions have added new financial and capacity stresses on primary care systems, with primary care physicians making decisions from an increasingly challenging position. The construct of prevention is central here. There is also a strong potential for the prevention of disability and frailty through multiple approaches: Treatment to decrease disease severity, preventions of additional diseases which could interact with preexisting disease, frailty prevention through maintenance and strength of exercise tolerance, and nutrition. Tertiary prevention such as rehabilitation after a stroke is critical to improve functioning and reduce disability. Overall, prevention could

substantially improve the health of older adults and could achieve such benefits with little or no additional lifetime medical spending.

As described by the WHO, success in the life-course requires investment in prevention of disease, disability, injury, and preserving health and wellbeing at each age and stage of life (Briggs, 2016). The WHO report on healthy aging is built around the concept of functional ability. The most recent WHO report as the health-related attributes that enable people to be and to do what they have a reason to value. It is this value of health partially mediates this interaction (Smith, 2018). The report by the WHO emphasizes that this prevention ability is determined by both the intrinsic capacity as an individual and the influence of the environments that they inhabit. This builds on capability-based approaches used in other areas. The report approaches the changes associated with aging in the context of the entire life-course that focuses on the second half of life: Functional gains are dependent on preventative behaviors.

Value of health, or lack thereof, is not the only barrier to preventative treatment. Only the poorest do not have access to service, necessitating policies which focus on expanding provisions to particular groups that are excluded or marginalized. When almost everyone does not have access to the service, wider ranging or universal strategies are usually required to be successful. Policies which aim at the level of social gradients and equal distribution of benefit can result in significant health benefits for older adults and improvement in health quality. For example, around 1 in 5 cases of AD worldwide is estimated to be attributed to low education attainment with about 6.5 million attributable cases globally in 2010 alone (WHO; Briggs 2016). This underscores the need for primary prevention strategies. In many settings, the pattern will fall somewhere between the two extremes and a combination of strategies will be needed with specific policies to increase access to care by older adults by taking into account of each national context.

The extent of the opportunities that arise from increased longevity will depend heavily on one key factor: Health. If people are experiencing these extra years of life with good physical and mental capacity and if they live in enabling environments, their ability to do the things they value may have few limits. If these added years are instead dominated by declines in capacity and disabling environments, the implications for older people and for society are much more negative. There is now a strong knowledge base that interventions work and matters at every age and stage of life. Some contents apply to every age, like physical activity, nutrition, and a healthy environment. Others are specific to an age. For societies, this approach is critical to decrease health disparities between individual's social, economic, and age groups in nations which develop accumulatively and can be predicted by exposures to each point in the life-course. Further, these investments will lay the basis for compressing morbidity into the latest stages. People who arrive at old age healthy are positioned to remain healthier into the older ages. This approach can lead to lower long-term healthcare costs and a healthier and more productive society.

Precision Medicine

Precision medicine is the intersection of person-centered care and prevention where clinicians examine individual variables to predict gaps in current interventions. What does this patient, and their specific biopsychosocial make-up, need to live a long a healthy life?Niederehe (2013) noted that it is time to move theory-based mode of research and to begin to conduct studies that actively test specific hypotheses about the psychopathology of interest. Ideally the goal would not be simply to replicate in older adults whatever findings have previously been shown about the psychopathology model in younger adults, but to relate aspects of the model to aging process variables – in other words, to examine how the aging process interacts with particular facets of psychopathology. Just focusing on dementia, Camille Carroll, a researcher in the field of translational and stratified medicine, says "dementia is a disease with so many different contributing factors it can be difficult to predict. There is strong epidemiological evidence that a number of cardiovascular and lifestyle factors such as hypertension; high cholesterol, diabetes, obesity, stroke, atrial fibrillation, smoking and reduced cognitive functional or social activities can predict the risk of dementia in later life, but no studies have taken place that allow us to see this quickly" (Jammeh, et al., 2018).

To represent the aging process in such studies, the research design might well incorporate variables drawn from relevant basic science theories of aging (biological, psychological, and social). Moving in this direction will help research become less merely

descriptive and more mechanistic by elucidating increasingly specific pathways whereby aging impinges on mental disorders. Concerns about psychopathology as a dimension, longitudinal studies, as well as looking a practical gaps and issues that are not currently being studied are of interest. Clearly older adults share the complex interplay among multiple interacting forms of disease. If all past, present, and future predictors and processes that contribute to future events were known and quantifiable, algorithms could be constructed that produce perfect risk estimates of individuals – that is, they would predict with perfect accuracy whether an event would occur or not in every individual.

However, technological advances will be needed to acquire such data. Currently, estimates of risk are incomplete and conditional on information that was included in risk calculation. This, however, is improving. Predictive analytics can improve the clinical care by providing general recommendations for populations that can be incorporated in clinical guidelines. This includes cognitive aging and depression especially. Predictive algorithms are an essential component of guideline recommendations. However, because predictive models imperfectly explain clinical outcomes, they do not estimate individual risk very well even when they accurately explain the group risks. Consequently, these models cannot replace a physician or healthcare provider in the process of everyday care. Again, according to Niederehe (2013), big data has entered the picture. The NIH has made high-resolution imaging procedures which sequence the individual genome, as well as psychosocial components, viable, and so team science has been involved (Martin, et al., 2016). In addition, there are studies that involve risk assessment and management involving risk calculators, as well as the science of behavioral change itself. Increasingly there is the personalization of care or precision medicine. Precision medicine is close.

Diabetes is one disease where this is having an impact with higher prevalence but less deaths. Precision medicine makes possible the prevention of the most individually salient risk factors. Some years ago, it became obvious that loss of executive function is a problem for adjustment. Mast et al. (2004) examined risk indicators associated with cerebrovascular disease, including diabetes, hypertension, and heart disease. Their relationship to depression and executive function was also assessed. Older adults were initially assessed at the time of admission to a rehabilitation hospital and 18 months thereafter. Persons with below-average executive function at baseline were more likely to develop depressive symptoms as they accumulated cerebrovascular risk factors. Among those with average or above executive function, the addition of risk factors did not lead to greater levels of depression. Thus, the causal risk factors were executive dysfunction with diabetes. Hypertension and heart disease were variable markers. However, the exposure rate of older primary care patients with diabetes, hypertension, and heart disease is substantial and may be conceived as a hierarchy of increasing risk for cerebrovascular disease and associated executive dysfunction. In summary, big data can point to vulnerabilities and prevention should begin when there are depressive symptoms among the population with cognitive and physical disability and vascular diseases.

Another population with an elevated prevalence of depression disorders involves persons with age-related macular degeneration. Rovner and Casten (2008) found a substantial reduction in the incidence of major depression and withdrawal from favored activities among older persons who received problem-solving therapy compared to those who received routine care and depression assessments only. Persons with the diagnosis of macular degeneration in one eye were approached for study participation at the time of diagnosis of macular degeneration in the second eye. Although the groups were nearly free of depressive symptoms at the onset of the study, those that reported depressive mood were more likely to develop a depressive disorder. Presence of any level of depressive mood increased the risk of developing a depressive disorder by 16-fold. The presence of insomnia doubled the risk also. Those randomized to problem-solving therapy received six 45 to 60-minute in-home sessions for 8 weeks. At 8 weeks, 23% of those in the routine care had diagnostic criteria for major depression compared to 11% in the intervention group. This held up to six months. Although the preventative effect of problem-solving therapy on depressive mood was limited to the 2-month intervention, reduction disability carried over up to 6 months and fewer than 1 in 10 patients declined to complete the 8-week intervention.

Finally, Smit et al., (2006) followed a population-based cohort of more than 2,000 adults ages 55 to

85 over 3 years to detect the emergence of clinically significant depressive symptoms. Also collected was an array of demographic, functional, biomedical and psychosocial characteristics thought to predict the incidence of depression among older community residents. This data allowed them to construct a parsimonious predictive model of risk indicators, including female gender, low education, 2 or more chronic conditions, functional limitations, small social network, and depressive symptoms at baseline. This model accounted for 80% of the risk for clinically significant depression. Depressive symptoms at baseline accounted for half the risk. In order to prevent the depressive symptoms from progressing into a clinically significant case, 16 people needed to be treated. However, when the group's baseline depressive symptoms were restricted to include only those with small social networks and functional limitations, the number needed to treat dropped to 5. This clearly made this a practical intervention.

Overstating the potential benefits of precision medicine is difficult. However, there are concerns. There are three fundamental reasons why precision medicine might not improve the health of populations. First, disease pathogenesis, especially for common non-communicable diseases, is extraordinarily complex. This is additionally complicated by an apparent association between the multiplicity of specific genes and conditions including obesity, hypertension, and cancers. Second, the heterogeneity of disease etiology will make precision prediction even more complex. Third, for population wide change to occur many individuals must alter their behavior based on these health outcome predictions. Behavior modification is operationalized well, but relatively few patients find it valuable enough to enact.

Value of Clinical Therapeutic Trends

The meta-trend in this case presents in the full application of precision and preventive medicine where older adults are recognized as diverse individuals with a lifetime in insults which complicate clinical work. This complication is not negative, but instead requires different considerations. Professional societies are taking notice at the policy level. There has been a spate of guideline papers from the American Psychological Association regarding older adults (APA, 2014). Several of these speak to aging and assessment, emphasizing how clinical work with older adults involves developmental issues specific to late life; a cohort perspective considering comorbid physical illnesses, problems with polypharmacy, cognitive and sensory impairments and history of mental of medical disorders. Aging is of course a reflection of the interaction of the person with the environment. Often there are no mental health services for older adults, which is an obvious shortcoming. There is no shortage of research implicating the health impact of mental illness and stressors do not decrease with age. This battle is unfortunately often played out with medications according to the medical model. The APA notes that work with older adults is most effective if considered within certain guidelines (listed below). These competencies are focused on individual background with a holistic approach: there are certain issues specific to the aging population while others are considerate of individual background and development. This follows the precision medicine approach discussed previously.

Competence in and Attitudes toward Working with Older Adults

General Knowledge About Adult Development, Aging and Older Adults.

- This includes diversity and knowledge about biological and health related aspects of aging

Clinical Issues

- Cognitive Changes—PET is now approved as is the yearly physical and cognitive evaluation
- Functional Capacity – everyday competence with IADLs especially
- Psychopathology at Late Life – 20% plus of older adults will meet criteria for an Axis I disorder.

Assessment and Treatment

- Relevant methods involve clinical interviewing, self-report scales, cognitive performance measures, direct behavioral observation, role playing, psychophysiological techniques, neuro-imaging, and use of informant data.

- Interdisciplinary assessment is optimal.
- Knowledge of normal aging is important.
- The integration of objective measures of cognitive performance includes historical, neurological, psychiatric, medical and other diagnostic information.
- The older adult's premorbid functioning is a needed and important area of evaluation for determination of current problems, especially cognitive ones. Knowledge of education, occupation, current interests,and cognitive practices are all relevant
- Psychometric theory, test standardization, and the importance of using reliable and valid measures.
- Norming is messy and critical. No assessments are validated for older adults on personality or psychophysiological assessments are noted.
- Knowledge of the brain is more important than other areas of focus. Special targets for research including biomarkers will be more important each year as algorithms improve.
- Knowledge of function is critical. This includes ADLs and IADLs and their interaction with cognitive skills and the environment.
- Cross cultural issues are very relevant and often prepotent in determining outcomes. Considerable within and between group differences can be found. Multicultural competence includes explicit consideration of the older adults ethnic, racial, and cultural issues. Multicultural issues and aging are linked.
- Use of other informants is also important and requires a context for best understanding.
- Repeated assessments may be required.
- Use of performance-based evaluations are important.
- Assessments are also needed for specific issues like competence in various areas. Targeted evaluations are necessary.
- Accommodations are also important and need both study and consideration
- Knowledge of the core psychotherapies are most relevant for assessment. This involves an evaluation of outcomes but more specifically these involve psychotherapy-specific outcomes (e.g., CBT and thinking).
- Telehealth may be increasing but has been applied sparingly to older adults.

American Psychological Association, 2014

Effective application of therapeutic practice to the aging population obviously requires a different set of considerations. However, few major advances have been made in development of psychotherapeutic technique since the early 1970's. These guidelines present a step in the right direction. Psychotherapy in recent years has been largely medicalized with the emergence of health and medical psychology. These guidelines are understanding that fact. Attempts to operationalize therapy, however, disregard the significant impact of individual differences. As we have intimated above, turning psychotherapy into a technology modeled on medicine has limited the cultural scope and conceptual depth. In the past research was conducted and a vigorous professional debate ensued while schools of therapy emerged promoted by founders who were genuinely impressive. Now the field is at risk of becoming overly-fragmented, specialized, and driven by the DSMs. In research, niche investigations directed applications of extent methods to smaller and more trivial questions have become all too numerous.

In previously mentioned work, Hyer (2014) focused psychological treatment of older adults on five domains: cognition, health, depression, anxiety, and life adjustment. The Watch and Wait model is case-based care. This involves a plan, applying information,

validation, assessment, and a program of treatment modules. The belief is that a careful and slow process of care is an improvement over the fast-paced primary care and psychiatry clinics. The therapist does not pick one best treatment at the outset. Mistakes are often made at the gate (see table below on Failure Points). Problems actually better confess themselves over time. According to the model, patients are carefully assessed and a monitored. The patient is given hope, a humane context through psychoeducation, support, and a belief that change will occur with careful preparation. In 3-5 sessions, the health care provider recognizes how the patient presents with and experiences the five problems, validates and builds alliances, provides necessary psychoeducation, carefully selects treatment options, applies objective measures for a treatment response, and monitors. Changes are made with equal deliberation. One does not get better if the person does not have preparation for and then "experience" in the intervention. We also know that in the complex treatment of older adults, success depends on patient beliefs, organized extra-therapy variables, as much as the actual treatment plan and monitoring.

Failure Points

- Deciding too quick to initiate care
- Under-dosing
- Inadequate trial duration (6 weeks necessary)
- Frequency of follow up
- Lack of monitoring
- No team or family involvement
- Wrong Rx: Depression and SSRIs or CBT
- Insufficient time: Noncompliance with meds, dropout of psychotherapy
- Wrong dosage: Too little or not in the "window"
- Interference from other Rxs: Med side effects
- Adherence issues: Pt does not do tasks
- Complex families
- Use of substances: Opioids, other meds
- Wrong diagnosis

The complexity of science then as it applies to psychotherapy reflects a background of elemental human understanding that is prior to and underlies the scientific endeavor. Psychotherapy is an activity that is not theoretically grounded given a proper definition of theory, nor does it emanate from the comprehension of scientifically established underlying causal entities or explanatory mechanisms. What we call psychotherapy outcome research is from pharmaceutical research, which is par with industrial product testing or educational program evaluation (Woolfolk, 2015). The diagnostic classification framework utilized was not predicated on highly developed science. DSMs were theoretical and entirely based on observed co-occurring clusters of symptoms. They have never understood how the etiology or pathophysiology of anxiety differs from depression and the way that physicians understand diseases. We know very little about how the SSRIs affect the brain, much less than we know about how antibiotics affect bacteria. The research findings that have not clarified either the causal mechanisms underlying the disorders or mechanisms in which the drugs produce their effects are not there. For example, there are RCTs showing that a single disorder of major depression is ameliorated not only by SSRIs, but also is treated effectively by such an incredibly wide array of diverse medications that they cannot possibly all operate on the same mechanism. This lack of specificity is true for drugs as well. Some individual SSRIs seem to be somewhat effective in RCTs for a wide variety of disorders; that makes no sense to infer that all the

different diagnoses are underlain by a single unitary pathophysiology. Some naturalistic investigations further call into question the common assumption that maintenance on anti depressants prevents relapse (see Woolfolk, 2015).

But something works. We highlight this back-view of psychotherapy because it works, without knowing exactly why. It then leaves much to be desired but is also a method of care that optimizes the chances of a better quality of life. Outcomes consistently show that with behavioral change and emotional resilience, anything is possible. But we exist in the real "scientific world" of clinical care. Evidence-based care sloppily attempts to integrate with a person-center approach. Within psychology there are several projects to codify empirical behavioral treatments. These have included the Journals of Clinical Psychology: Science and Practice (Scogin et al., 2005) and a special edition of Psychology and Aging (Ayers et al., 2007; Gallagher-Thompson and Coon 2007; Longsden, McCurry, and Teri 2007; Scogin 2007; Yan and Scogin 2007). Division 12 of the APA provides evidence-based resources for numerous disorders from their readily accessible website: div12.org. Additionally, Meiskowski and Scogin (2014) have also updated the empirically supported treatment issues for depression, anxiety, insomnia, and dementia. Meiskowski and Scogin outlined the importance of late life anxiety, depression, insomnia, disruptive behaviors with individuals with depression, caregiver interventions, and evidence-based strategies for enhancing memory and cognitive function. There have also been several books to place aging psychosocial therapies and interventions in some perspective regarding clinical outcomes (e.g., Lichtenberg, Mast, Carpenter, & Wetherell, 2015).

Unified theories of psychotherapy, often anchored to CBT, suggest several strategies involving restructuring of maladaptive cognitive appraisals, changing action tendencies associated with problematic emotional experiences, preventing emotional avoidance, utilizing emotional exposure procedures, as well as emotion-focused interventions, which emphasize the functional nature of emotions, facilitating emotional approach and tolerance, and emotional regulation. Research which has been based on the general adult populationmay not provide the same outcomes in this older population. Regardless, these modules have been borrowed and now are the bread and butter of psychotherapy for older adults.

Fortunately, common factors in therapy contribute to change which can generalize (Norcross, 2015). We also have the structure of the therapy itself. Culturally appropriate adaptations are essential to matching treatment to the individual's cultural and moral guide. Therapeutic relationships are built on the patient's belief that the therapist is caring and competent. Makover (1992) long ago noted that continued alteration of the therapy leads to a better "approximation of truth."Review of the therapeutic processes and treatment outcome consistently seems to reveal that the quality of the patient's participation is most determinate of outcome. What the patient does in this setting and outside of the therapy determines how well the therapy will go. If the patient buys into the model – competent therapist, some behavior change, empathic reactions, and monitoring –, change stands a good chance. Change can be acceptance of the status quo and a renewed commitment to living. Perhaps a more accepted view of the change agents that enhance the change process involves the following:

Strategies to Keep Patients on Track

- Educate patients about their role
- Incorporate patient's preferences into decision making
- Increase investment in therapy
- Help plan for the end game: Discussing an endpoint increases commitment
- Provide education about patterns of change: Watch out for fast gains or temptations to bolt
- Strengthen early hope: Instill optimism
- Enhance motivation for treatment
- Use Motivational Interviewing
- Foster treatment alliance: Be empathic
- Use the team
- Discuss treatment progress: Use objective self-reports

Jamie Chamberlin (Monitor on Psychology, April, 2015)

Therapy is people helping people with fixed belief systems, encouraged behaviors, and some rituals. Techniques may actually be mostly placebo delivery devices, though they also provide some clarity and guidance in a nebulous process for both therapist and patient. Interpersonal empathy is at the heart of the change in most conditions. It is co-constructed by mutual responses that activate similar cortical and subcortical neural circuits between clinicians and patients (Preston et al. 2002). It is also noteworthy that accurate empathy reflects and creates a synchronizing interpersonal neural biological attunement (Nummenmaa et al. 2012). Functional magnetic resonance imaging has demonstrated that when verbal communication is accurately comprehended in speaker/listener dyads, it is correlated with the emergent neural coupling of spatial temporal brain activity (Stephens et al. 2010). Patients in pain who are treated by an emphatic physician experience less pain (Jensen et al. 2014). There is evidence to support that psychotherapeutic talent, ability, and skill matters for effective treatment. Connecting with a patient on an empathetic level improves the relationship and promotes change. Perhaps we need to develop a new intellectual framework for research and to conduct a reexamination of various conceptual levels, at which causal mechanisms are conceived. Alternatives emphasize the human side of therapy and an ecological contextual understanding of human beings.

Agreed Upon Therapeutic Positions or Intenverntions

1) good communication skills that include Rogerian qualities empathy, warmth, and non-judgmentalism,

2) the ability to make clients feel that they are understood by the therapist,

3) the capacity to form an effective working relationship with the client,

4) the ability to provide an explanation of the client's distress that is consistent with the interventions to be provided, acceptable to the client, and useful in the provision of therapeutic benefit,

5) the ability to develop and articulate a plan of treatment that is consistent with how the client's problems are explained and with the conduct that promotes health,

6) the ability to inspire confidence in the client and to be persuasive in convincing,

7) the capacity to faithfully monitor the patient's progress,

8) flexibility with regard to treatment options,

9) the capacity and willingness to confront difficult material in the therapy, even material that may be especially upsetting to the client,

10) the ability to maintain client morale and motivation given the impediments and effective treatment that arise during therapy,

11) the broad awareness of the client's and the therapist's personal characteristics contextual grounds, for example ethnicity, social economic status, physical health, and how these factors directly and interactively affect the capacity of therapeutic change,

12) the judicious management of interjecting the therapist's own reactions to the client to ensure that these reactions can be rationally expected to have a beneficial effect,

13) being well informed and staying abreast of the latest research on biological, social, and psychological bases of the client's problem, and

14) being desirous and active at improving one's therapeutic skills, coupled with the ability to obtain usual feedback, to self-reflect, and to modify one's conduct in therapy based on self-reflections.

Purpose in Life

Geriatrics, as a biopsychosocial model, must also account for how one evaluates their own life. Considering one's life to be meaningful is associated with a variety of adaptive mechanisms. Self-reports on meaning are associated with higher quality of life, especially with age, superior self-reported health, and a decrease in mortality. Meaning in life predicts slower age-related cognitive decline and a decreased risk for AD (Hooker, Masters, & Park, 2018). Meaning in life is associated with lower incidence of psychological disorders and suicidal ideation and are more likely to rely on adaptive coping techniques. Meaning in life converges on the idea that purpose and meaning in life matter as one possesses a sense of significance (Boyle, et al., 2010). Meaning in life is also associated with social connection, of positive mood, an environmental pattern that is acceptable, and coherence, as well as several cognitive constructs. Fortunately, from large representative samples and bodies of research, using different definitions of meaning in life strongly support the conclusion that life is rated as meaningful, especially as one gets older. It might even be that meaning in life is essential to survival in the same way as sunlight or calcium.

In the Common-Sense Model of Leventhal et al. (2015), the meaning assigned to symptoms is a product of a process in which symptoms are matched and linked to one another, underlying the prototype or model of the illness. The meaning created by this match activates expectations as to how a symptom is judged and the intervention will affect the underlying condition. The hypothesis that symptoms and functional changes are mapped or linked to prototypes is a central assumption of the Common-Sense Model. Indeed, mapping is an active process that is both intrapsychic and interpersonal. It is familiar to people. It is our "prototype checks," that we make continually to monitor somatic and functional experience consciously or unconsciously and compare these experiences with underlying prototypes both of the self and of specific illnesses.

Psychological wellbeing is entrenched in several constructs that add to life quality. Most happiness is internally developed, involving an internal simulator that allows the person to be happy. We create our own happiness internally. Barbara Fredrickson's broaden and build theory (2004) provides that over time positive emotions accumulate to build multiple resources and support to our wellbeing. Joy leads to being urged to play; interest causes the desire to seek new information; pride makes you think big; elevation inspires you to feel better; and love makes you want to share and explore. A construct of meaning has also been much involved with issues of savoring, gratitude, meditation, learned optimism, resilience, positive connections, as well as a sense of vitality. The person develops a sense of strength from strength and can respond positively to his or her environment. This involves training that is attached to any one of these constructs.

Flourishing is another concept which emerges in this discussion. This occurs when the individual is optimally happy with positive emotions suffusing meaning in life. An abundance of research in the areas of wellbeing, such as happiness, positive emotions, strength, optimism, hope, flow, mindfulness, love, wisdom, courage, creativity, authenticity, motivation, and goals have been evaluated. The estimation is that the equation for happiness involves roughly 40% voluntary control, or lifestyle. Seligman noted that happiness is involved in pleasure, engagement, and meaning itself; pleasure being a feel-good factor, engagement meaning the depth of involvement, and meaning being the purpose of what is being done.

Resilience is another relatedconstruct; it allows the person to have a sense of emotional awareness, impulse control, optimism, causal analysis, thinking, empathy, self-sufficiency, as well as reaching out. Resilience appears to have an important role in shaping whether or not people recover from adversity and sustain healthy growth and functioning at later life. High levels of wellbeing protect against elevated levels of inflammation, decrease the likelihood of disability and early mortality, and helps older people manage the negative impact of health changes. Factors such as mastering and self-efficacy are negatively correlated with increased ADL and IADL limitations. Proactive coping has a negative impact on disability and self-efficacy is associated with increased disability. People with higher levels of resilience appear to suffer from fewer ADL limitations and have improved physical functioning. Perhaps this is partially related to the fact that people who are more resilient also engage in physical activity.

One perspective on this is subjective age: if one is as old as they *feel.* A younger subjective age has been shown to contribute to positive personality development and more positive expectations of better actual cognitive functioning in older age (Voss,et al., 2018). Subjective age also predicts better memory performance, as well as slower decline in performance. Although perceived health has been tied to both subjective age and cognitive functioning, only a few studies have examined the relationship between subjective age and cognitive performance. In one such study, the MIDUS study, participants who reported younger subjective age performed better on two cognitive factors 10 years later (Stephan, et al., 2014). In that study subjective age was found to predict cognitive performance above and beyond chronological age, as well as the participants' health measured by chronic disease burden. How one perceives self matters.

Purpose in Life (PIL) also leads to life satisfaction. Although life satisfaction is typically considered relatively consistent across time, it may change in response to life circumstances, such as divorce or unemployment. Some people may adapt more readily to new situations, and thus appear to have relatively stable life satisfaction. Others may not adapt as quickly. All things considered, how successful one is in life might depend on how one views life satisfaction. Over the course of several studies, researchers seem to learn that as participants' life satisfaction increased, the risk of mortality is reduced by a considerable amount, as much as 20%. PIL orchestrates these reactions in life.

This un-biological construct seems to have benefit in ways not expected. Individuals who report greater PIL in their lives appear to be less likely to develop diseases, especially AD or its precursor, mild cognitive impairment (Boyle, et al., 2010). Participants' PIL can be measured by the level of agreement with such statements as "I see a good life; I can think of what I have done in the past and what I hope to do in the future," or "I have sense of direction and purpose in my life." After an average of four years and a maximum of seven years of annual follow-up clinical evaluations, 155 of 951 participants developed AD. Controlling for other related factors, greater PIL was associated with substantially reduced risk in developing AD, as well as a reduced risk of mild cognitive impairment and slower rate of cognitive decline.

Religion is one way to establish meaning in life. The literature distinguishes between three types of religiosity: Organizational, non-organizational, and intrinsic. Organizational religiosity typically involves public or group activities and is most commonly measured by one's religious service attendance. Non-organizational religiosity by contrast is more private and typically occurs on the person's own time alone, encompassing activities, such as reading religious text, praying, and meditating. Intrinsic religiosity is concerned with individual subjective meaning of religiosity and how religious beliefs affect everyday life. Research demonstrates that religious involvement of any type benefit clinically depressed individuals. Depressed symptoms have been shown to decrease across time in persons engaged in organizational religiosity. Ronneberg, Miller, Dugan, and Porell (2016) found that organizational and non-organizational forms of religiosity affect depression outcomes in different circumstances. Important strategies to prevent and relieve depression among older adults may include improving access and transportation to places of worship among those interested in attending services and facilitating discussions about religious activities.

Starting with the work of Pargament (2013), scholars have increasingly conceptualized broad benefits arising from religion and stress mitigating effects. Those studies link a strong sense of divine control with lower psychological distress among older Americans and religious attendance with more self-reported tranquility. Such engagement may also foster stress-buffering network connections with multiple studies indicating that individuals who attend religious services at least once a week receive more social and emotional support. This church-based social capital may also enhance psychological resilience and coping capacity in the face of life challenges. This is especially true in late life when individuals suffer a generalized loss of social and physical assets.

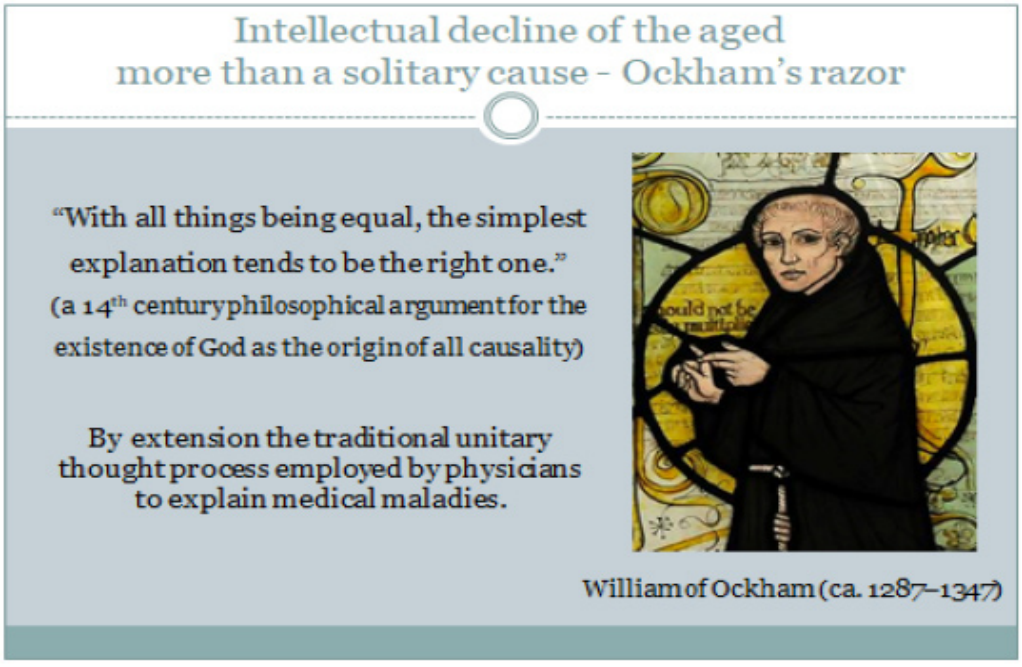
Despite its stress-buffering implications, linkages between religious attendance and biological weathering remain unexplored. Bio-demographic literature suggests that weathering pressures on the three linked physiological subsystems of aging, inflammatory, metabolic, and cardiovascular can be influenced. Emerging literature in the anthropology and neuropsychology of religious literature also suggest that emotionally charged group activities may also be beneficial.

We note here one last feature in purpose in life, personality. This is the scaffold that provides the filter the older adult to act. Personality provides the structure for the form of adaptation. It is the central determinant of dealing with life, of a person's vison and of meaning in life itself. Importantly as people age, the trait characteristics are influenced and assist in the later lifespan issues. Personality is then a friendly construct that allows for an understanding of the consistency of a person's behavior through stress and non-stressful times. This occurs across the lifespan. It provides clarity of treatment action in managed case formulations. Personality traits in particular represent one non-genomic area of consideration in the formation of consistent behaviors based on a broad swath of genetic and environmental factors. They also may indicate susceptibility to cognitive dysfunction long before noticeable clinical signs. In sum, they provide a window into the logic of the patient's actions and patterns of behavior. It is indeed a deep phenotype of intra-personal and extra-personal activity.

We believe that later life behavior from cognition to affect is influenced by one's personality. Personality is a heuristic construct that unfolds the person in subtle and loud ways. They are not diseases. They are complex and intra- and inter-active, and are understandable reflectors of the person, habits that are often unduly rigid. Given the models, the patterns are also logical. They are persistent, but decipherable. Interestingly, personality at later life alters in slight ways with age. Personality bends but does not break (heterotypic continuity). Personality grows the person and is also responsive to the ravages of living – health declines of all sorts. What's more, the construct of PD has many miles to go before its final understanding. In time, research and wisdom will reveal this. For now, it is a presence that allows us as health care providers to as a good a glimpse into personhood and behavior as possible.

Conclusion

The biopsychosocial diathesis stress model posits that there are certain interconnected biological, psychological, and social factors that can affect an individual's predisposition to mental health problems, say depression. These include factors that serve either as potential protective factors that can act as buffers against life's problems or risk factors leading to problems. Our science is fledgling and we are learning quickly. Factors contribute to health across the spectrum are being identified: social, physical, and psychological. We are now taking action; often we get in our own way. Older adults require more coping help in the form of lifestyle markers and structural assists in the form of health, education, and good habits. We are getting better. In tis context Ockham's Razor does not help very well. Rarely is their one or a simple cause for anything, certainly when psychopathology is concerned.



These metatrends impact case formulation of the identified patient and his/her milieu and life. Better understanding of the complexity of the human brain is providing new answers and complicating results daily. Epigenetics especially fosters new trends by applying technological advances with precision. It opens up our vistas. The biopsychosocial model additionally provides a framework for understanding this complexity in assessment and treatment. Trends in understanding the aging brain as a new entity instead of an aged version of a younger brain (aging is more complex than mere deterioration of structures). Most notably, lifestyle factors offer a plethora of intervention points identified by precision medicine and prevention efforts. Precision medicine allows us to pin-point specific areas of intervention for individuals, and not populations of patients. Prevention intends to decrease the overall burden on healthcare and improve quality and quantity of life. Therapy itself has changed little, but our understanding of its better principles allows us to apply it to the aging population with some focus and merit.

We have lamented that, compared to other age groups, older adults have the highest numbers of doctor visits, hospital stays, and prescription medication usage. Left unchecked, healthcare expenditures will likely rise from the current level of ~15% to 29% of gross domestic product (GDP) in 2040.Symptoms and changes in function and deviations from the underlying image or self-prototype are the subjective online cues that are the targets of much of patient self-management, a relevant variable here.

The metatrends then are biopsychosocial bank in the truest sense. They play out in all cases of older adults. The nuances of problems are unreasonably high in number. Psychosocial problems are heterogeneous in causal formation. And, there are significant differences in response to treatments, to side effects among classes of medications, especially psychiatric ones. Fortunately, we do have increasing "powers" (i.e., precision medicine, prevention, etc.).Older adults are individual and complex. They are also understandable and changeable.

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Citation: **Lee Hyer, Lauren Lee, Sarah Maginga, Joe Sam Robinson.** *Meta-Trends in the Holistic Care of Older Adults. Open Journal of Geriatrics. 2018; 1(1): 33-72.*