

Chapter 5  
**Cognitive Decline of Aging:  
 Important Neuroendocrinological Predictors of  
 Early Cognitive Decline in A Clinical Setting**

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**ABSTRACT**

This paper sheds light on a hidden epidemic that is the precursor to widespread disease: mild-moderate cognitive impairment (MCI). Although it is commonly considered to be a consequence of the normal aging process, cognitive decline frequently begins as early as 30, starting with a slowing of processing speed that then affects memory and attention, and leads to numerous diseases including obesity and depression. Decades pass in this impaired state before the patient experiences the first clinical symptoms of dementia. The Brain Evaluation and Assessment Method (BEAM) for diagnosing cognitive impairment will be introduced, along with a new paradigm for “dementia” and how it develops. Potential methods for diagnosing, preventing, and reversing cognitive decline and the myriad diseases associated with it will be discussed.

**INTRODUCTION**

MCI is a heterogeneous disorder, affecting different people in different ways and to different degrees of severity. Some cases of MCI turn into Alzheimer’s dementia, some remain mildly impaired, and others are reversed.

The general consensus is that dementia takes 20 years to develop. That is simply not true – dementia takes at least 40 years to develop. The process begins with the development of pre-MCI at around 30 years old, which is mostly asymptomatic but marked by a slowing of brain processes (which can be measured by the P300 brain wave, discussed later). The first symptoms of MCI then usually become apparent 15-20 years later (a “foggier” memory and slightly impaired attention span) and it may then take another 20 years for MCI to become dementia. By the age of 70, most people are cognitively impaired, and half of all 85-year-olds have dementia. The results of a study by Plassman *et al* on the prevalence of dementia in the United States are shown in the middle of Figure 1. The right column shows our predictions of the prevalence of MCI. It is common knowledge that Alzheimer’s is becoming an epidemic, but not many people seem to realize that MCI already is. MCI is more prevalent in the United States than dementia, yet it is often ignored. Thus, people could be suffering from the symptoms of MCI for decades before they are diagnosed with dementia.

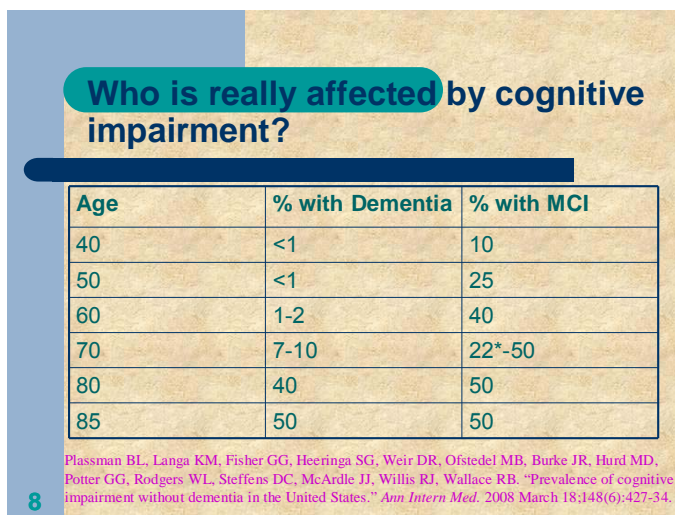


Figure 1. Prevalence of cognitive impairment and dementia in the United States.

Most people would be worried if their doctor told them that their obesity, high blood pressure, and bad lipid profile were steering them toward an impending heart attack or stroke. Most people would want to prevent such an outcome – and they would want their doctor to help. But patients should also be very concerned if their doctor says that they have a slow or fatigued brain. Insomnia and anxiety should also be cause for concern, because they often mark the beginning of brain decline, because they trigger the decrease in processing speed that precedes cognitive decline and the plethora of diseases that may result. As brain disease progresses, verbal and visual memory skills will decline, as will attention, working memory skills and IQ. In the end you are left incapacitated by dementia.

There are five brain problems that cost the United States at least \$100,000,000,000 (one hundred billion dollars) or more per problem. They are: obesity, addictions, neuropsychiatric disorders, violence, and cognitive impairment. Most people don't realize it, but their weight, mood, level of anxiety, depression, insomnia, and likelihood to become violent, are all the physiological manifestations of what is going on in the brain. Additionally, many people are not aware that brain disease does not always manifest itself in obvious ways. The reality is that when a person dies of heart disease "caused" by obesity, they really died of brain voltage deficiency. When a patient dies of an alcoholic liver, he really died of chronic GABA deficiency. All of our autopsy statistics are fraudulent because they don't deal with the antecedent deterioration of brain functioning. So when a smoker dies of lung cancer and the autopsy form says "death due to lung cancer," that is not really the root cause; death was actually due to dopamine and acetylcholine deficiency, which lead to the cigarette addiction, ultimately resulting in lung cancer.

### Diagnosing Cognitive Decline

There is no standard method for diagnosing cognitive decline. Many different techniques have been employed over the years, including: neuropsychological tests, neuroradiological techniques, and laboratory testing (APOE4 and dopamine genotypes, Beta amyloid protein, etc). We are proposing a new standard based on the work of Clark Randt and many others. This new standard is the Brain Evaluation and Assessment Method (BEAM).

By using the BEAM we can produce a "brain print" for each individual. This helps us to identify the degree of cognitive impairment present. In effect, it enables us to determine the patient's cognitive age. Figure 2 shows how different mental processes are affected by the aging process. Verbal ability is typically the last skill to go, which is why we still see people running for President in their 70's.

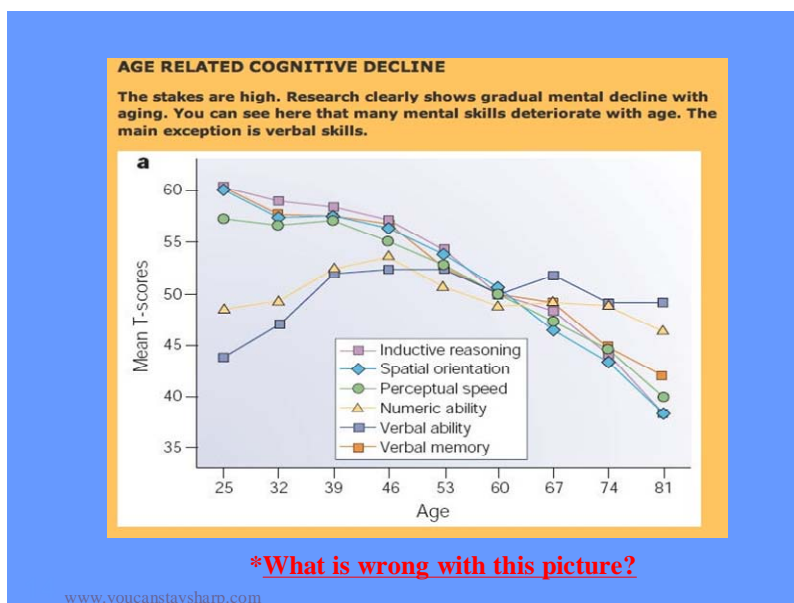


Figure 2. This graph illustrates how many mental skills deteriorate with age. The only real exception is verbal ability, which remains relatively constant throughout adulthood and fools many individuals into thinking that they have not yet entered into cognitive decline because they are still verbally superior.

Determining a person's cognitive age is similar to determining their cardiac age – you need to have similar information about the brain to what you already have for the heart. You need to assess the electrophysiology of the brain. Of particular importance in this assessment is the P300 wave (to be described in more detail later), whose latency in milliseconds denotes brain processing speed, and voltage indicates the brain's "power." This wave should become the "cholesterol test" for the brain. In addition, you need to assess memory and attention. You need to be aware of the patient's temperament and type because that affects their cognitive style, and you need to assess their psychiatric state (e.g. through the Millon Clinical Multiaxial Inventory) and their IQ. Once you have this information you can make appropriate recommendations for the prevention, treatment, and reversal of virtually every chronic disease.

A major problem we have when attempting to diagnose cognitive decline is a lack of cognitive baseline measurements. Doctors keep regular check of their patients' blood pressure, so if a patient's blood pressure has consistently been 100/70 and suddenly shoots up to 170/100 it will be cause for some concern, while also giving the doctor some idea as to what the problem might be. Someone with a blood pressure of 90/50 may be going into hypovolemic shock or they may be very athletic – but constant monitoring of the baseline levels makes this determination simple. We don't have these baseline measurements for the brain. Therefore, if you are interested in your patients' cognitive health you should start obtaining baseline and ipsative data right away – memory, attention, brain processing speed, voltage. See brain print below:

<b>Brain Print</b>	
<b>Case Study: JB 60yo Male</b>	
MRI – Brain	Mild atrophy
P300	384 (greater than 20 ms over age)
Voltage	3.8
AEP	2
VEP	3
EEG	Mild disorganization – mild slowing
WMS	80/92/104/108
TOVA	+C, 440
CNSVS	Poor cognitive flexibility, memory
MMSE	16

Figure 3. Brain print of JB, a 60-year-old male.

Figure 3 illustrates a typical brain print. In this case it is JB, a 60-year-old male. First of all we can see that the MRI showed that the patient has mild atrophy of the brain. Secondly, we measured JB's brain speed (as measured by the latency in milliseconds of the P300 wave), and that enabled us to determine that JB has the brain speed of an 84-year-old. Next, we measured voltage – which in a healthy brain would be 10 mV; the voltage of JB's brain is equivalent to that expected in a 72-year-old. From the evoked potentials (AEP and VEP) we were able to determine that JB has the brain stability of a 50-year-old. The EEG should be completely organized; however the report shows that JB's had mild disorganization and mild slowing. Next on the brain print are results of the memory scales. JB's verbal memory score is in the 10<sup>th</sup> percentile and suggests that he has the verbal memory of a 90-year-old brain. JB's visual memory (e.g. for remembering faces) is akin to that of a 70-year-old. The third figure, for immediate memory, is equivalent to that of a 50-year-old, and the fourth figure, for working memory, is equivalent to that of a 40-year-old. The attention scores (as measured by the Test of Variables of Attention (TOVA)) are deficient as well. Many older people are dangerous on the road because the processing speed of their brain is poor – their reaction time is typically around 400 ms. The rest of the

print shows that JB has poor cognitive flexibility and memory. The last category on the print is the Mini Mental State Examination (MMSE), which is a dementia scale. JB scored 16 out of 30, which is suggestive of severe cognitive impairment.

**Brain Print**  
**Case Study: JB 60yo Male**

Test	Before Reversal	After Reversal, 1 year
P300	384	340
Voltage	3.8	5.2
AEP	2	1
VEP	3	NL
EEG	Mild disorganization, slowing	NL – mild slowing
CNSVS	Poor flexibility, memory	NL – significantly improved
WMS	80/92/104/108	>95
TOVA	+C, 440	NL
MMSE	16	28

Figure 4. Brain print of JB, a 60-year-old male, before and after reversal.

Obviously, the outlook for JB seemed bleak. However, the good news is that I have been able to reverse at least some brain dysfunction in all of my patients. If we look at Figure 4, we can see that with JB we achieved an improvement of 44 ms of brain speed – an improvement of brain youthfulness equivalent to 40 years, an improvement of brain voltage equivalent to 14 years, an improvement of brain stability equivalent to 30-40 years, an improvement of 10 to 20 years in terms of memory, and an improvement of probably 50 years of mental status as measured by the MMSE.

**A New Brand of Neuropsychiatry**

- **Axis 0: Anatomical:** MRI, PET, etc.
- **Axis I: Electrophysiological:** speed, voltage, rhythm, synchrony
- **Axis II: Memory function -- IQs**
- **Axis III: Attention function**
- **Axis IV: Personality, temperament, and psychiatric diagnoses**
- **Axis V: Interfacing medical problems – endocrine, vascular, metabolic, genetic etc.**

Figure 5: Neuropsychiatric axes.

Brain prints such as JB's are constructed along the lines of a new set of neuropsychiatric axes that serve as a guide for integrating brain function with the function of all other organ systems. These are much more comprehensive than the DSM psychiatric axes. See Figure 5.

Most doctors are well versed in the electrophysiology of the heart, but when it comes to the brain, few know even the simplest facts. The brain is the body's number one electrical organ. The main parameters that should appear on a brain print are electrophysiological ones: speed, voltage (power), rhythm, and synchrony. The second layer includes the four forms of memory, which are evaluated by the Wechsler Memory Scale (WMS). You can also add parameters for long-term, verbal, visual, spatial, immediate, and working memory. Finally, there is the MMSE to evaluate a global dementia score. In every disease some of these measurements will be deficient. We need to establish baselines so we can distinguish what is normal for each individual (just like monitoring blood pressure to differentiate between hypovolemia and athleticism).

### Decline in Processing Speed

A decline in processing speed is the earliest marker of cognitive deterioration. This decline sets off a cascade of changes leading to declines in memory, attention, IQ, and changes in temperament. The human body reacts to light at 1/120<sup>th</sup> of a second, sound at 1/10<sup>th</sup>, pre-thought at 1/120<sup>th</sup>, and it thinks at 1/3<sup>rd</sup> of a second. The processing speed of a person with dementia is 4/10<sup>th</sup>, whilst that of a person in a deep coma is 1/2 a second. Every doctor should monitor brain processing speed as often as they monitor cholesterol and blood pressure.

As mentioned previously, brain speed can be measured by the P300 wave. The P300 wave is an event-related potential that can be recorded via EEG as a positive deflection in voltage at a latency of roughly 300 plus age (in years) milliseconds. The presence, magnitude, topography, and time of this signal enable us to measure processing speed, voltage, rhythm, and synchrony. The P300 test of brain speed is functionally the cholesterol test of the brain. Someday, we envision that just as how most Americans know their cholesterol levels, everyone will know their brain age, and how many years they are away from dementia. Cholesterol, the first precursor in the steroid hormone pathway and a marker of decline in our steroid manufacturing, is a tremendous global marker of both heart disease and physical wellbeing. Brain processing speed delay is antecedent to both memory and attention decline, and global effects on our body systems, and it will become the marker that everyone wants to know.

## P300 latency, voltage, WMS-III, MMSE by decade

**Table 4**  
Characteristics and mean (SE) of P300 latency, voltage, WMS-III, and MMSE by decade

Parameter	Age 1-10 (N=32)	Age 11-20 (N=44)	Age 21-30 (N=98)	Age 31-40 (N=197)	Age 41-50 (N=328)	Age 51-60 (N=318)	Age 61-70 (N=191)	Age 71-80 (N=216)	Age 81-90 (N=78)	Age 91-100 (N=4)
P300 latency	324.4±7.2	327.2±4.2	317.6±2.0	328.0±2.4	332.8±1.5	339.3±1.6	347.9±2.0	359.9±2.2	371.6±3.8	368.5±15.1
P300 voltage	8.0±0.9	7.5±0.4	7.4±0.3	7.3±0.3	6.3±0.2	6.3±0.2	6.0±0.2	6.0±0.2	5.8±0.4	7.2±2.5
Verbal	98.5±6.8	94.8±4.5	101.7±2.8	100.0±2.1	100.9±1.6	102.8±1.7	101.1±1.9	95.4±1.9	88.7±2.9	86.7±6.4
Visual	99.7±11.6	97.8±6.0	101.5±2.9	96.5±2.2	97.1±1.5	99.3±1.8	92.7±1.7	89.0±1.8	85.5±3.5	86.3±2.3
Immediate	90.5±9.2	96.6±6.3	101.7±2.9	99.2±2.0	98.4±1.8	101.8±1.9	95.8±2.0	90.7±1.9	84.6±3.3	83.7±5.0
Working	87.0±11.1	91.1±3.2	98.8±2.4	96.7±2.0	94.9±1.3	94.8±1.6	92.0±1.5	91.5±1.7	88.7±2.3	82.3±1.3
MMSE	18.9±3.2	28.0±0.6	26.7±1.3	26.9±0.8	27.2±0.5	26.6±0.4	27.0±0.4	26.5±0.4	22.9±0.9	22.5±1.3

"P300 (latency) event-related potential: an accurate predictor of memory impairment." Braverman ER, Blum K. *Clin Electroencephalography*. 2003 34(3):124-39

Figure 6. Characteristics and mean (SE) of P300 latency, voltage, WMS-III, and MMSE by decade.

Figure 6 shows the characteristic and mean (SE) of P300 latency, voltage, WMS-III scores, and MMSE scores by decade. The average 21 to 30-year-old has a brain speed of 317 ms, and it can be seen that with each decade brain speed slows by between 4 and 10 ms, so that by the time a person reaches their 80's their brain speed has slowed to 371 ms. This figure also shows that voltage decline is slower than brain speed decline, which is why people can still work at 70. They rely on effort to overcome speed.

Figure 7 shows the relationship between MMSE score and brain speed. This figure shows that a poorer MMSE score is associated with a slower brain speed. For example, people with a MMSE score of 0-19 (indicative of moderate to severe cognitive impairment) were found to have a mean (SE) brain speed of 375 ms, whereas those with a MMSE score of 28-30 (no cognitive impairment) were found to have a mean (SE) brain speed of 350 ms.

	P300 Latency (Mean ± SE)	P300 Voltage (Mean ± SE)	Verbal (Mean ± SE)	Visual (Mean ± SE)	Immediate Memory (Mean ± SE)	Working Memory (Mean ± SE)
Group A MMSE 0-19, age ≥40, N=24, (P<0.0001)	375.0±9.0 NS*	6.7±0.7 NS	77.5±6.8 NS	64.1±8.2 NS	65.2±7.1 NS	67.5±3.3 NS
Group B MMSE 20-24, age ≥40, N=64 (P<0.0001)	368.6±3.5 P=0.004	6.4±0.4 NS	81.4±2.7 NS	80.3±2.7 NS	77.7±3.3 NS	78.8±2.0 NS
Group C MMSE 25-27, age ≥40, N=109 (P<0.0001)	354.8±3.1 NS	6.2±0.3 NS	90.9±2.3 NS	85.2±2.1 NS	83.6±2.3 NS	86.7±1.7 NS
Group D MMSE 28-30, age ≥40, N=189	350.8±2.0 NS	6.0±0.2 NS	101.9±1.6 P=0.0001	94.6±1.8 P=0.001	98.2±1.7 P=0.00001	95.1±1.6 P=0.00062
Group E Control, age ≥40, N=489	343.4±1.3 P=0.0004	6.0±0.1 NS	103.4±1.3 NS	98.9±1.3 NS	101.9±1.3 NS	96.5±1.1 NS

\*NS = Not Significant. P Values are comparisons of B to A, C to B, D to C, and E to D.  
\*\* WMS-III demographics: A (N=11), B (N=44), C (N=68), D (N=123), E (N=205)

P300 (latency) event-related potential: an accurate predictor of memory impairment Braverman ER, Blum K *Clin Electroencephalography*. 2003 34(3):124-39

Figure 7. The P300 (latency) event-related potential is an accurate predictor of memory impairment.

The theory of brain speed does not only explain dementia, it also offers an insight into autism. When a baby is born they have “high voltage cognitive impairment” – high voltage but low speed (See Figure 8). Nobody remembers anything about the day they are born because essentially we are all born demented! In normal circumstances, a developing child’s brain speed increases, voltage normalizes, and cognitive skills improve. In children with autism, brain speed does not increase to the same extent, and they remain cognitively impaired, and thus are developmentally delayed. Their brains are like airplanes that do not pick up enough speed to lift off the ground. What do doctors give autistic children? They prescribe amphetamines, antidepressants, and hormones – all of which help to speed up the brain. When they reach puberty, children are hit with tons of steroids that speed up their brain accelerating them into adulthood like a rocket taking off. And for the old person, gravity pulls them down and they retire, or at least their brain speed does.

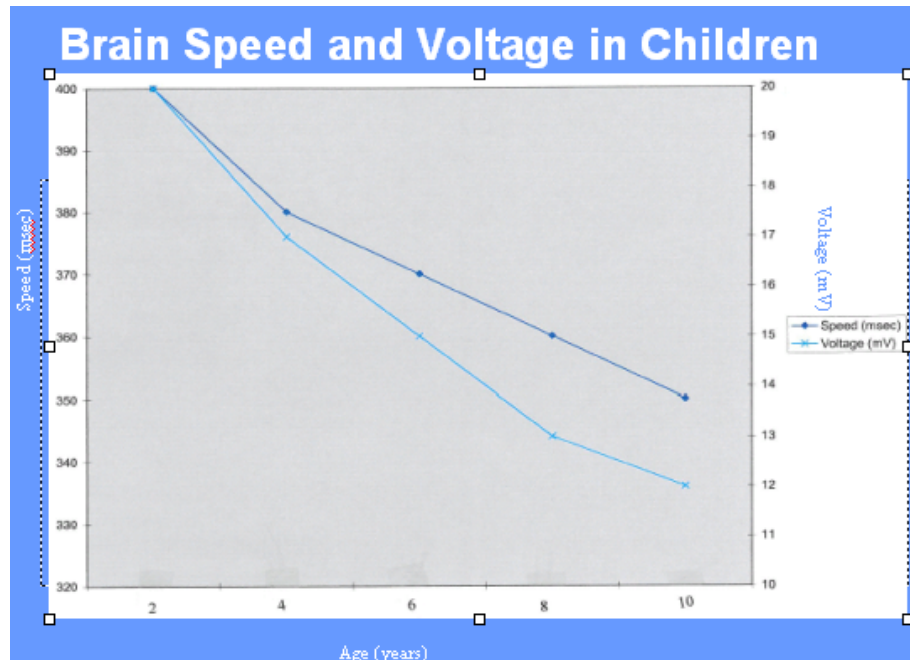


Figure 8: Brain Voltage and Speed in Children

## PREVENTION AND TREATMENT OF COGNITIVE DECLINE

We no longer have to accept dementia as a normal consequence of aging. There are four lines of defense we can take to treat, prevent, and reverse cognitive decline so that we can live up to our full potentials into old age. The first is our lifestyle choices, including social circles, sleep habits, living environment, etc. The next is diet, nutrition, and supplementation. Third is hormone replacement with bioidentical hormones. And the last is drug therapy. While we know that many prescription medications interact directly with the brain, we tend to forget that each of these lines of defense affects the neurotransmitter systems of the brain. Having knowledge of the electrophysiological functioning of our brains can help us understand how our neurotransmitter systems are functioning, and this can help us make decisions about which lines of defense to follow.

### Neurogenesis

When I was in medical school I was told that we cannot grow new neurons, but now we know that we can. We are now learning that antidepressants and some hormones stimulate neurogenesis, or the growth of new neurons, and this may explain how they increase brain speed. While much research is still to be done on this, the implications from the discovery of neurogenesis may mean that we can gain even better cognitive function as we age, and grow smarter as we grow older.

### Hormones and Brain Speed

Hormones have the potential to increase brain speed. It is no coincidence that brain speed increases significantly around the age of 13 when steroid hormone levels take off. As mentioned before, some hormones are associated with neurogenesis. In the section about neurogenesis in *Kaplan and Sadock's Synopsis of Psychiatry* two factors that stimulate neurogenesis are discussed: antidepressants and growth hormone. Both are associated with cognitive enhancement including increased brain speed.

Many other hormones that are associated with increases in brain processing speed are also associated with neurogenesis. Human growth hormone (HGH) and pregnenolone appear to be the most effective at restoring the brain; however thyroid hormone, estrogen, DHEA, and numerous other hormones are also thought to be beneficial. (Figure 9)

## Bioidentical Hormones that may Potentially Impact Cognitive Decline:

- Androstenedione
- Calcitonin
- Dehydroepiandrosterone (DHEA)
- DHEA-Sulfate (DHEA-S)
- Erythropoietin
- Estriol
- Estrone
- Human growth hormone (HGH)
- Hydroxycortisol/aldosterone
- Insulin-like growth factor (IGF)
- Incretin (at least 50% bioidentical)
- Insulin
- Melatonin
- Parathyroid Hormone
- Pregnenolone
- Progesterone
- Testosterone
- Thyroid: T3, T4
- Vitamins D2, D3
- Oxytocin
- DDAVP

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Figure 9. Bioidentical hormones that may have an impact upon cognitive decline.

### Parathyroid Hormone

Levels of parathyroid hormone increase with age. We have found a positive correlation between P300 latency and parathyroid levels. Hyperparathyroidism and osteoporosis can lead to the development of calcifications throughout the body and the brain. Calcification in the brain is correlated with impaired brain processing speed. This suggests that control of parathyroid levels may be an important factor in the prevention of age-induced dementia. This can be accomplished counter-intuitively – through supplementation with PTH. It most likely triggers a negative feedback loop on itself leading to lowered endogenous production of PTH. The increasing amount of evidence that is suggestive of a link between bone, behavior, and the brain has led to an entirely new field of medicine called neuropsychosteotology.

### Estrogen

Estrogen replacement therapy in menopausal women leads to a significant improvement in information processing as indexed by a significant shortening of P300 latency. Estrogen has been shown to interact with the cholinergic system and is in essence a cholinergic hormonal drug. If you take out a woman's ovaries you are effectively sending a woman into partial dementia – she will instantly lose 10 ms of brain processing speed. The menopause has the same effect on cognitive decline. So, it is important to remember that cognitive decline is accelerated in women, and therefore women tend to get dementia at a younger age than men and at a higher rate.

### Testosterone

As a man ages, his testosterone levels drop dramatically. Testosterone, and other androgens, help to regulate beta-amyloid protein, which accumulates in the brain of Alzheimer's patients. Testosterone replacement therapy may therefore be used to prevent Alzheimer's disease and other forms of cognitive decline.

### Thyroid Hormone

Hypothyroidism is associated with poor concentration, memory disturbances, depression, and decreased cognitive function. It is also linked to increased P300 latency. Thyroid hormones have been shown to modulate adult hippocampal neurogenesis in studies in rats.

## Growth Hormone

Research has shown that growth hormone replacement therapy decreases P300 latency. Growth hormone is probably the greatest chemical that we have for reversing cognitive decline. Growth hormone should never have been called growth hormone – repair hormone is a far more accurate name.

## Melatonin

Melatonin deficiency deprives people of antioxidant protection, and also results in loss of sleep and/or poor sleep quality. Sleep deprivation has been shown to increase P300 latency.

## CONCLUDING REMARKS

Cognitive decline has been associated with almost every medical illness, including: diabetes, sickle cell disease, thyroid disorders, metabolic syndrome, and cancers, to name a few. The good news is this: improvement of cognitive decline can occur with reversal of illness throughout the body, as well as electrochemical imbalances in the brain. Our view is that brain testing allows the early stages of cognitive decline to be identified between the age of 30 and 40. Furthermore, this decline is reversible with evidence-based treatments. Fifteen productive years can be added to every individual's working life, and perhaps more importantly, these fifteen years can bring new learning experiences and happiness.

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