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Plasma growth hormones, P300 event-related potential and test of variables of attention (TOVA) are important neuroendocrinological predictors of early cognitive decline in a clinical setting: Evidence supported by structural equation modeling (SEM) parameter estimates

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Abstract A review of the literature in both animals and humans reveals that changes in sex hormone have often been associated with changes in behavioral and mental abilities. Previously published research from our laboratory, and others, provides strong evidence that P300 (latency) event-related potential (ERP), a marker of neuronal processing speed, is an accurate predictor of early memory impairment in both males and females across a wide age range. It is our hypothesis, given the vast literature on the subject, that coupling growth hormones (insulin-like growth factor-I, (IGF-I) and insulin-like growth factor

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binding protein 3 (IGF-BP3)), P300 event-related potential and test of variables of attention (TOVA) are important neuroendocrinological predictors of early cognitive decline in a clinical setting. To support this hypothesis, we utilized structural equation modeling (SEM) parameter estimates to determine the relationship between aging and memory, as mediated by growth hormone (GH) levels (indirectly measured through the insulin-like growth factor system), P300 latency and TOVA, putative neurocognitive predictors tested in this study. An SEM was developed hypothesizing a causal directive path, leading from age to memory, mediated by IGF-1 and IGF-BP3, P300 latency (speed), and TOVA decrements. An increase in age was accompanied by a decrease in IGF-1 and IGF-BP3, an increase in P300 latency, a prolongation in TOVA response time, and a decrease in memory functioning. Moreover, independent of age, decreases in IGF-1 and IGF-BP3, were accompanied by increases in P300 latency, and were accompanied by increases in TOVA response time. Finally, increases in P300 latency were accompanied by decreased memory function, both directly and indirectly through mediation of TOVA response time. In summary, this is the first report utilizing SEM to reveal the finding that aging affects memory function negatively through mediation of decreased IGF-1 and IGF-BP3, and increased P300 latency (delayed attention and processing speed).

Keywords Structural equation modeling (SEM) · P300 latency · TOVA · IGF-1 · IGF-BP3 · Age and memory

Introduction

Studies demonstrate that all individuals between the ages of 50 and 80 experience some form of mild cognitive impairment and in many cases, numerous cognitive changes. Most (as much as 50%) progress to advanced dementia by age 80. During this time (age 50–80) of progressive cognitive decline few, if any, memory assessments are performed by physicians. As a result, dementia has now become the 8th leading disability in the United States.

Many hormones in the body also decline as we age, with certain exceptions. Those that decline include insulin-like growth factors, testosterone (males), estradiol (females), dehydroepiandrosterone (DHEA) and its sulfate, Triiodothyronine, 1,25(OH)2 Vitamin D, inhibin, arginine vasopressin and pregnenolone. Those that increase with age include insulin, vasopressin (basal), cholecystokinin, atrial natriuretic peptide, norepinephrine, epinephrine, FSH, LH (women and some men), parathormone, cortisol, activin (males) and prolactin (males) (Morley and van den Berg 2000).

The question arises, are the hormonal changes antecedent to the cognitive decline; not related to the cognitive decline; or occur as a result of the changes in the brain? Numerous studies support the hypothesis that hormonal decline contributes to the cognitive changes in the brain.

The progression to full blown dementia includes, loss of brain processing speed, decline in memory and attention function, personality and temperament change, IQ changes, and ultimately, the inability to perform daily tasks. It is noteworthy that the impact on declining brain process is influenced by hormone deficiencies including growth hormone (Messier et al. 2004; Kalmijn et al. 2000a,b; Modrego and Ferrandez 2004; Mahajan et al. 2004; Pandian and Nakamoto 2004; Brooke and Monson 2003; Polleri et al. 2002; Aleman et al. 1999; Watanabe et al. 2004; Herrmann et al. 2004; Dumas et al. 2006; Gleason et al. 2005; Pinkerton and Henderson 2005; Honjo et al. 2005; Levine and Battista 2004), estrogen (Burkhardt et al. 2004; Bates et al. 2005; Falter et al. 2006; Hogervorst et al. 2004; Bremner 2004; Okun et al. 2004; Hoskin et al. 2004), testosterone (Moffat et al. 2004; Henderson and Hogervorst 2004; Rosario et al. 2004; Cherrier et al. 2005; Leblhuber et al. 2004; Bicikova et al. 2004; Yai et al. 2003; Weill-Engerer et al. 2002; De Bruin et al. 2002), DHEA (De Bruin et al. 2002; Brown et al. 2003; Ravaglia et al. 2002; Armanini et al. 2003; Rasmuson et al. 2002; Knopman and Henderson 2003; Hoskin et al. 2004; Hoskin et al. 2004; Bowen et al. 2002; Casadesus et al. 2005; Gregory and Bowen 2005; Arwert et al. 2005a,b,c,d), sex binding globulin and other hormones (van Dam 2005; Casadesus et al. 2006; Meethal et al. 2003; Shively and Bethea 2004; Pike 2001; Lim et al. 2003; Wolkowitz et al. 2003).

A review of the literature reveals that sex hormones (Cauley et al. 1989; Kalmijn et al. 2000a,b; Raynaud-Simon et al. 2000; Sherwin 2003; Kawas et al. 1997; Tang et al. 1996; Mulnard et al. 2000; Norbury et al. 2003; Kolsch and Rao 2000; Compton et al. 2001; Behl et al. 1997; Barrett-Conner and Goodman-Gruen

1999; Behl and Manthey 2000; Sano 2000; Cyr et al. 2000; Cholerton et al. 2002; Wang et al. 2000; Breltner and Zandi 2003; Smith and Levin-Allerhand 2003), DHEA (Tan and Pu 2001; Huppert et al. 2000; Leblhuber et al. 2004; Vallee et al. 2001; Murialdo et al. 2001; Pavel et al. 2003; Aleman et al. 1999; Arai et al. 2001; Petruzzi et al. 2002; Kalmijn et al. 2000a,b) and other hormones (i.e. growth hormones) have often been associated with changes in behavioral and mental abilities, memory, brain glucose utilization, neuronal function and dendritic architecture in both animal and human studies (Donahue et al. 2006; Grill et al. 2005; Sonntag et al. 2005a,b; Berton et al. 2006; Lichtenwalner et al. 2001; Ramsey et al. 2004; Shi et al. 2005; Lynch et al. 2001; Thornton et al. 2000; Shin et al. 2005). A series of studies by Sonntag et al. and others strongly suggests a relationship between GH and memory in animals, and provides a framework to evaluate possible relationships in the human as well (Kappeler and Epelbaum 2005; Sonntag et al. 2001; Brunso-Bechtold et al. 2000; Sonntag et al. 2000; Almeida and Barclay 2001). Additionally, the (GH)/IGF–1 axis is known to be involved in aging of physiological functions including, low levels correlating with cognitive decline (Almeida and Barclay 2001) as a function of age. In fact, GH deficiency, an important regulator of IGF-1, is associated with reduced well-being.

A recent Medline search revealed that evaluating IGF-1 can improve well-being in GH deficient adults (Asthana et al. 1999), as well as improve cognitive functioning by increasing brain processing speed (Baum et al. 1998; Rollero et al. 1998; Carro et al. 2002; Van Dam and Aleman 2004; Arai et al. 2001). IGF-1 may also play an important role in the speed of information processing and intelligence (Papadakis et al. 2005). Low IGF-1 levels were directly correlated with lower mini-mental state examination (MMSE) scores in patients with more advanced cognitive (Burman and Deijen 1998) and neuronal function deterioration (Arwert et al. 2005a,b,c,d).

In this regard, a meta analysis revealed that an overall relationship between IGF-1 levels and cognitive functioning in healthy elderly people exist (Arwert et al. 2005a,b,c,d; Binoux 1999). Finally, metabolic studies on insulin-growth factors have been intensively investigated (Baxter and Martin 1986; Arwert et al. 2005a,b,c,d; van Dam et al. 2005). It is noteworthy that a major function of growth hormones in the elderly involves a cellular repair mechanism potentially increasing neuronal connections (Demlin 2005; Leor et al. 2006; Li et al. 2006; Simpson et al. 2006).

In order to evaluate the interrelationships between plasma hormone levels, cognition, and memory, we utilized the P300 (latency) ERP. This electrophysiological marker of brain processing speed has been the subject of many neurocognitive studies (Braverman and Blum 1996, 2003; Braverman et al. 2006). Results suggest that genetic antecedents may control brain P300 functionality (Mulert et al. 2006; Gallinat et al. 2003; Nacher 2000; Comings et al. 1999; Hill et al. 1998; Johnson et al. 1997; Polich and Bloom 1999; Begleiter et al. 1998).

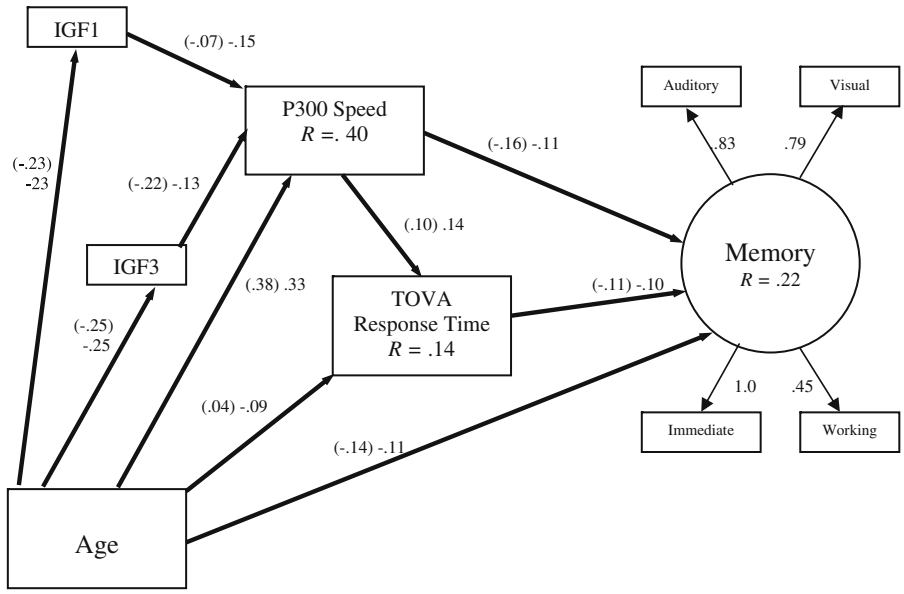
It is our hypothesis that the small percent of individuals seem destined to escape Alzheimer's Disease (AD), and their relative invulnerability may reflect both genetic and/or environmental factors, which may be related in part to sex hormones and the IGF-1 system (Khachaturian et al. 2004; Morley 2003).

Abnormalities on the TOVA have previously been shown to accurately predict impaired Wechsler memory scale-3rd edition (WMS III) scores and early dementia by our laboratory (Braverman et al. 2006). Thus, we have proposed earlier that the optimal mode for identifying patients at risk for dementia and/or AD would be to couple TOVA with other standard diagnostic techniques, i.e., MMSE, WMS-III, and P300 latency (Braverman and Blum 2003, 1996; Braverman et al. 2006). Screening patients for early dementia requires accurate characterization of attention failure in a clinical setting.

The aim of the present study is to quantify the relationship between plasma growth hormones, P300 ERP and TOVA as putative neuroendocrinological predictors of early cognitive decline in a clinical setting. Thus, structural equation modeling (SEM) parameter estimates were developed hypothesizing a causal directive path leading from age to memory mediated by estrogen, progesterone, testosterone, IGF-1, IGF-BP3, P300 speed, and TOVA.

Methods

In this SEM model, depicted in Fig. 1, age was used as the major independent, or *exogenous* variable, and



CFI = .96 *NFI* = .95 *RFI* = .90

N = 1372 Analyzed

Fig. 1 SEM of age on memory with mediating variables. The Pearson correlations appear within parentheses; the SEM coefficients, in the form of standardized regression weights, appear without parentheses. All coefficients shown are statistically significant beyond the 0.05 level (one-tail tests)

memory was used as the major dependent, or *endogenous* variable. Hormonal levels, P300 and TOVA were hypothesized as intervening variables.

Participants

A total of 1,545 patients participated in the study. Gender and age were recorded for these patients; 739 (47.6 percent) were male and 806 (52 percent) were female. Data taken from patients 40 years and older, M=52.73±SD=18.21. The average age for females was 53.74±SD=18.16 and 51.76±SD=18.22 for males. These patients were selected for study from an outpatient private medical/neuropsychiatric clinical practice and research foundation in New York City. Other than age due to missing data, only data for 1,372 of the original sample were analyzed utilizing the SEM.

All subjects signed an approved IRB consent form based on an approval from the PATH Foundation IRB committee (registration #IRB00002334) and ethics board approval from the PATH Foundation. The criterion for study inclusion was at least one P300 test for each patient. Trained EEG medical and psychometric technicians conducted the tests. All test interpreters were blinded to other patient results. All subjects were part of a catchment study involving brain electrical activity mapping and aging research.

Analysis of hormones

IGF-1 and IGF-BP3 were used as the hormone measures, shown in the model appearing in Fig. 1. This hypothesis was tested in the statistical analysis of the data described below.

Venipuncture was done in nonfasting subjects between 8:30 AM and 7:30 PM at baseline examination of the Path Medical Clinic Program. Blood samples were collected in 5-ml tubes containing a 0.5 ml sodium citrate solution. All tubes were stored on ice before and after blood sampling. Platelet-free plasma was obtained by –2-stage centrifugation (10 min at 1600 g at 4°C and 30 min at 7000 g at 4°C). Platelet-free samples were immediately frozen in liquid nitrogen and stored at −80°C. Assays were performed blinded to information on the subject. Plasma levels of estradiol and sex hormone-binding globulin were estimated with double anti-body radioimmunoassays (Bioreference Lab, New York, NY). As measures of the levels of bioavailable and free estradiol, testosterone, and nonprotein-bound estradiol, respectively, were calculated in the basis of hormone and binding protein levels, for the analysis of GH and IGF-BP3, the laboratory performed standardized procedures (Sodergard et al. 1982; van den Beid et al. 2000; Brondu et al. 1996).

P300 latency

All patients in this study were analyzed by the BEAM. A 24-channel EEG recorder was used according to previous studies in our laboratory (Braverman and Blum 1996, 2003; Braverman et al. 2006). The standard international 10/20 system of electrode placement was used. In addition, there were two electrodes on the earlobes, two EKG electrodes connected to the cervical spine, two supraorbital electrodes (EOG) and an electrocap. During BEAM data collection, digital EEG was recorded in a monopolar (LR linked ears left over right) and bipolar (LR 3,4 linked ears left over right) montage. Waveforms were averaged off-line, such that trials on which the EEG or EOG exceeded ±100 microvolts were rejected. Single-trial data also was subjected to an EOG correction procedure to remove any remaining artifact.

The computer averaged evoked potentials. The system mathematically adjusted the baseline to the average value of stimulus signal per channel. P300 results were read at the maximum voltage (dV differential voltage; amplitude is relative to the mean voltage of the entire waveform) electrode (i.e. usually at PZ). Neuropsychiatric patients frequently have peaks that occur at FZ, CZ, OZ, P3, P4, O1, and O2. Review by a neurologist showed our computerized QEEG-P300 test to be 100% inter- and intra-reliable.

TOVA

TOVA was developed in the 1960s and the current version number 7 was released in 1997 (Manor et al. 2004). The visual TOVA is 21.6 minutes in duration and its lengthy run allows it to effectively measure attention deficit as a continuous performance test (CPT). In the visual form, a square flashes on the screen for 1/10th of a second in two-second intervals. As a person sits in front of the screen, a small box appears either on the top of the square or the bottom of the square. If the small box appears on the top, it is labeled as the target, and if at the bottom, it is labeled as the non-target. Each time the target box appears, the person is instructed to press a small, accurate microswitch. Every time the non-target box appears, the person is instructed to refrain from pressing the microswitch. Each patient begins with a 1-minute practice test and is instructed to take the test as accurately, quickly, and consistently as possible without mistake. An omission error signifies the times the patient failed to click the microswitch at the correct time. A commission error signifies the number of times the patient clicked the microswitch at the wrong time. Response time result is the amount of time that the patient took to answer. Variability result is a measure of the consistency of the patient's responses. In order for a score to be significantly deviant (SD) on the TOVA, it has to be less than –1.33. The TOVA score has to be less than –1.0 in order to be considered significantly deviant or borderline (SD-BL). TOVA results are age adjusted.

Memory

WMS-III is the standardized measure we used to assess learning and memory abilities in this study. Results are organized into summary index scores reflecting verbal, visual, immediate and working memory.

Statistical analysis

A path analysis or SEM was conducted to ascertain whether age influences memory through mediation of hormonal level, P300, and TOVA. SEM is a procedure used to statistically control for mediating effects when intervening variables occur in the research design (Bollen 1989; Maruyama 1997; Loehlin 1992; Long 1983). Once a zero-order correlation is found between two adjacent variables (X and Y) in such a model, SEM decomposes the coefficient into direct, indirect, total, and spurious effects. Often, what originates as a high correlation between X and Y proves to be null once the mediating effects of I are statistically controlled. In such cases, it is said that the effect of X on Y is indirect, mediated by I.

When all variables in the model are linked with one-another, the model is said to be full. When linkages are omitted, the model is said to be restricted. A key feature of SEM is its test of the statistical accuracy in omitting any set of linkages. The issue is addressed by multiple goodness of fit indices measuring the amount of variance explained in the

dependent variables with and without the linkages included. Moreover, contemporary fit indices are least susceptible to the bias associated with confirmatory factor analysis involving a large number of measured variables. With this in mind, the most widely used statistical index for this test is the comparative fit index (CFI) (Bentler 1990). A CFI of 0.95 or higher indicates that the amounts of variance would be the same, and that therefore, in the interest of economy, the linkages in question may be omitted from the analysis. Three indices of fit were given: the CFI, the relative fit index (RFI) (Bentler 1990) and the normed fit index (NFI) of Bentler and Bonett (1980). Once a final model is identified, these fit indices were provided to show the model was an adequate fit for the data, if not, they were not included in the model.

The present SEM procedure involved a hybrid structure including both a measurement model for memory (a hypothesized factor composed of auditory, visual, immediate and working memory measures), and the structural model shown in Fig. 1.

On the basis of the above review of the literature, this model hypothesized negative effects of increasing age on IGF-1, IGF-BP3, P300, TOVA, and memory. The model also hypothesized negative effects of prolonged latency of P300 and TOVA decrements on memory. It is noteworthy that when there is a prolongation of P300 latency there is also TOVA decrements independent of age, as neuronal processing with prolonged P300 latency attention processing slows down. Both have a negative effect on memory. Antecedent to this decline of neuronal and attentional processing appears to be hormonal growth hormone factor loss. Since these hypotheses were unidirectional in form, the model was tested using one-tail tests of statistical significance.

Results

Although age exerted an influence on both testosterone (β=−0.11, df=1, p<0.05) and estrogen (β=−0.24, df=1, p<0.05), no effects of testosterone or estrogen on P300 speed, TOVA, or memory were found. For testosterone these effects were β=−0.04, df=1, p>0.05, β=−0.03, df=1, p>0.05, and β=−0.01, df=1, p>0.05, respectively. For estrogen, they were β=−0.06, df=1, p<0.05, β=−0.05, df=1, p>0.05, and β=−0.08, df=1, p>0.05, respectively. These tests were asymptotic Z tests (with no degrees of freedom). Further, the GFI, CFI, and NFI scores forcing the non-significant testosterone and estrogen were 0.85, 0.78, and 0.65, respectively, indicating a decrease in the goodness of fit when estrogen and testosterone are included in the model. Given these findings, testosterone and estrogen were not considered further in the analyses of the data.

The correlation matrix of the variables in the study appears in Table 1. The means and standard deviations appear in Table 2, and the SEM outcomes appear in Fig. 1.

In Fig. 1, the Pearson correlation coefficients appear within parentheses; and the SEM coefficients, in the form of standardized regression weights (β), appear without parentheses. Only SEM coefficients statistically significant beyond the 0.05 level are displayed in Fig. 1. The model displayed a good fit of the data (*CFI*=0.96, *NFI*=0.95, *RFI*=0.90) showing the justification in leaving out the parameter estimates where IGF-BP3 predicts memory linkage.

The factor loadings of auditory, visual, immediate and working memory measures of the memory factor were 0.83, p<0.05, 0.79, p<0.05, 1.0, p<0.05, and 0.45, p<0.05. These loadings were derived from the correlations

Table 1 Correlation matrix

	1	2	3	4	5	6	7	8	9
1. Age	1.00								
2. IGF1	−0.225	1.00							
3. IGF3	−0.246	0.055	1.00						
4. P300SPEE	0.377	−0.146	−0.215	1.00					
5. TOVA	0.040	−0.015	−0.023	0.106	1.00				
6. Immediate	−0.065	0.025	0.037	−0.171	−0.120	1.00			
7. Working	−0.028	0.011	0.016	−0.075	−0.052	0.459	1.00		
8. Visual	−0.050	0.019	0.028	−0.132	−0.092	0.810	0.353	1.00	
9. Auditory	−0.052	0.020	0.030	−0.138	−0.097	0.847	0.369	0.651	1.00

Table 2 Summary statistics

	Age	IGF1	IGF3	P300	TOVA	Auditor memory	Visual memory	Immediate memory	Working memory
Mean	52.73	182.3319	3.38402	340.3854	.54	99.90	95.25	97.17	94.02
Std dev	18.215	100.13261	1.149586	35.95276	1.150	19.482	20.033	21.833	16.810
Std error	.47	4.20	.05	.91	.04	.71	.73	.79	.61

of the four components of memory. The SEM hypothesized are identifying the construct of memory. These factor loadings mean that each measured component of memory had a strong (r>0.45) correlation with the single construct of memory.

The model explained 5% of the variance in memory, which may not be clinically relevant to which the contribution by age was β=−0.11, p<0.05; that by P300 was β=−0.11, p=0.05; and that by TOVA was β=−0.10, p<0.05. The model also explained 2% of the variance in TOVA, which may not be clinically relevant to which the contribution by age was β=−0.09, p<0.05; and that by P300 was β=0.14, p<0.05. The model explained 16% of the variance in P300, to which the contribution by age was β=0.33, p<.05; that by IGF-BP3 was β=−0.13, p<0.05; and that by IGF-1 was β=−0.07, p<0.05.

As evidenced by the above findings, an increase in age was accompanied by decreases in IGF-BP3 and IGF-1; an increase in P300 latency; a decrease in TOVA response time; and a decrease in memory. Moreover, decreases in IGF-BP3 and IGF-1 were accompanied by an increase in P300 latency, and an increase in the latter was accompanied by an increase in TOVA response time. Finally, an increase in TOVA response time was accompanied by a decrease in memory. P300 influenced memory both directly and indirectly through mediation of TOVA.

Discussion

With regard to the present study it is noteworthy through a literature review, that binding sites for GH and, in particular, IGF-1 contribute to the function of certain brain areas (Sodergard et al. 1982). For example, several studies found that GH and IGF-1 contribute to the function of the hippocampus, a brain structure important for the maintenance of cognitive functions such as learning and memory (Pavel et al. 2003). Evidence for cognitive deficits in GH-deficient individuals has been found in several studies, some of which have shown that these deficits can be reversed by GH replacement therapy.

As previously noted, based on available data, one might hypothesize that relative GH or IGF-1 deficiency could contribute to the deterioration of cognitive function observed in the middle aged and elderly. Evidently, it appears that free testosterone levels negatively correlate with prolonged P300 latency especially in older men. These findings could have very significant importance in targeting both prevention and treatment of cognitive dysfunction in both males and females. Moreover, in other unpublished studies from our laboratory, we found a statistically significant relationship between age, memory, P300 and TOVA, with DHEA using SEM.

The present study does not reject the possibility that exogenous estrogens (Braverman et al. 2005; Dumas et al. 2006), testosterone, DHEA, and GH replacement may be beneficial in protecting against cognitive decline and AD, as a protectant against cell loss, as an antioxidant and as a protectant against other negative hormonal effects on brain function, including depression which may contribute to memory loss (Lobie et al. 2000; Heijer den et al. 2003; Burkhardt et al. 2006; LeBlance et al. 2001; Ellwart et al. 2003).

One important caveat in this study involves the percentage of clinical relevance using this SEM model whereby only 5% of the variability in memory is explained by these significant and important factors. Because the goodness of fit indices are greater than 0.90, it appears that much of the remaining 95% of variability in memory is either random error or other important factors such as genetics (other factors have not been adequately addressed in this proposed model). This is not to say that better models will not

be found in the future and warrants intensive investigation. Moreover, the goodness of fit indices for the figure are all above 0.90 indicating a better fit for the model without estrogen and progesterone. The coefficients are not significant for estrogen and progesterone and the goodness of fit indices are reduced when these coefficients are included in the model. For these reasons, we leave estrogen and progesterone out of the model.

We believe that the primary objective of diagnostic evaluations is to determine the most appropriate targets for and efficacy of therapeutic interventions. Our objective here is to add multifactorial physical and statistical diagnostic correlatives to confirm, question, refute and/or clarify the diagnostic conclusions derived from conventional procedures and assessments, thereby improving the focus of targeted therapeutic interventions, especially as it relates to age related neurocognitive decline. In this regard better methodology is required in a clinical setting to predict potential AD.

Summary

It has been suggested that utilization of P300 latency, a potential inheritable factor (Mulert et al. 2006; Gallinat et al. 2003; Nacher 2000; Comings et al. 1999; Hill et al. 1998; Johnson et al. 1997; Polich and Bloom 1999; Begleiter et al. 1998; Berton et al. 2006), is an important marker for detecting cognitive dysfunction in GH deficient patients with Sheehan's syndrome. It was proposed that these results must be performed on healthy patients to assess the clinical use of this electrophysiological method in the diagnosis of cognitive dysfunction due to GH deficiency.

In keeping with this suggestion, to our knowledge this is the first study to support the interactive role of growth hormone and other hormones and brain processing speed in humans attending a primary care facility. This takes on increased importance, when it is coupled with the recent finding that higher midlife free IGF-1 may be associated with better late-life cognition (Okereke et al. 2006)

We propose, based on this SEM, that primary care medicine directed at both the prevention and early diagnosis of dementia should be changed to emphasize the importance of coupling plasma hormone levels, with an electrophysiological marker such as P300 latency and TOVA decrements in response time as diagnostic tools.

This is the first study using SEM to reveal that age affects memory function negatively through mediation of decreased IGF-1 and IGF-BP3, increased P300 latency and prolonged TOVA response time.

Essentially, brain processing speed is antecedent to declines in memory and attention. It also appears that insulin growth factors, IGF-1 and IGF-BP3 (the precursor of GH), may be antecedent or concomitantly related to declines in attention and brain processing speed. This means that individuals who are approaching this wide spread epidemic of cognitive decline between the ages of 50 and 80, may need monitoring with psychometric testing and neuropsychological testing, as well as hormonal therapy.

Finally, our data support the contention that insulin-like growth factors, P300 ERP and TOVA, are important neuroendocrinological predictors of early cognitive decline in a clinical setting but interpretation of these interesting results must await further intensive investigation.

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Conflict of interest statement We declare that we have no conflict of interest. Eric R. Braveman MD, is the director of PATH Clinics where he utilizes both the P300 and TOVA as diagnostics, and Kenneth Blum, PhD is the scientific director of the PATH Research Foundation and is a paid consultant.

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