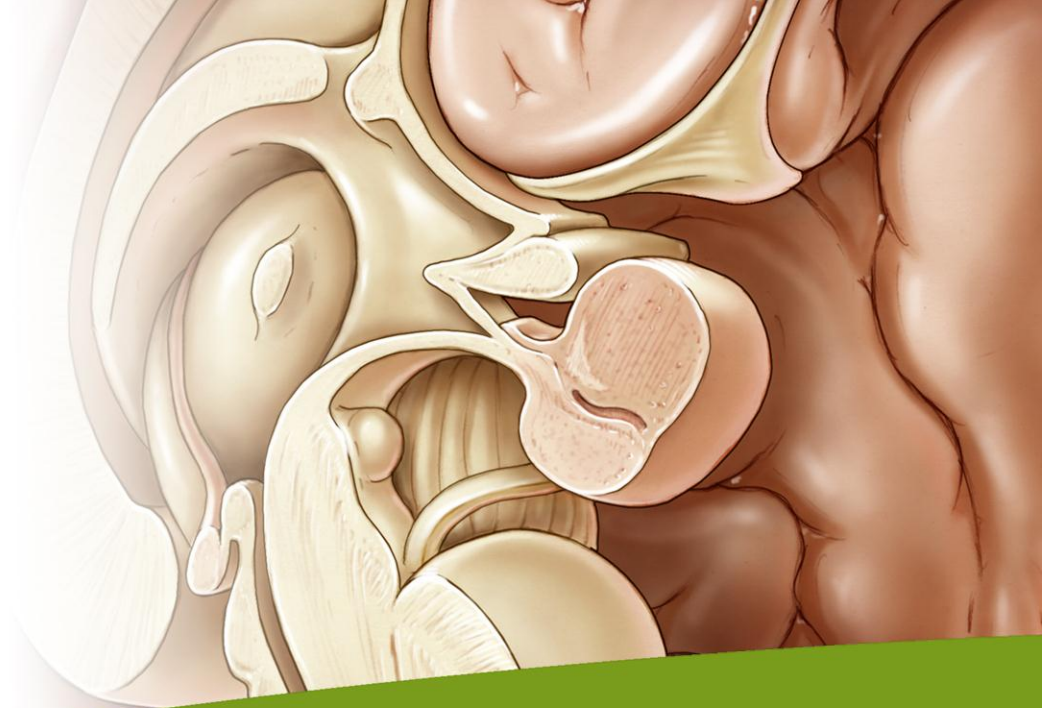


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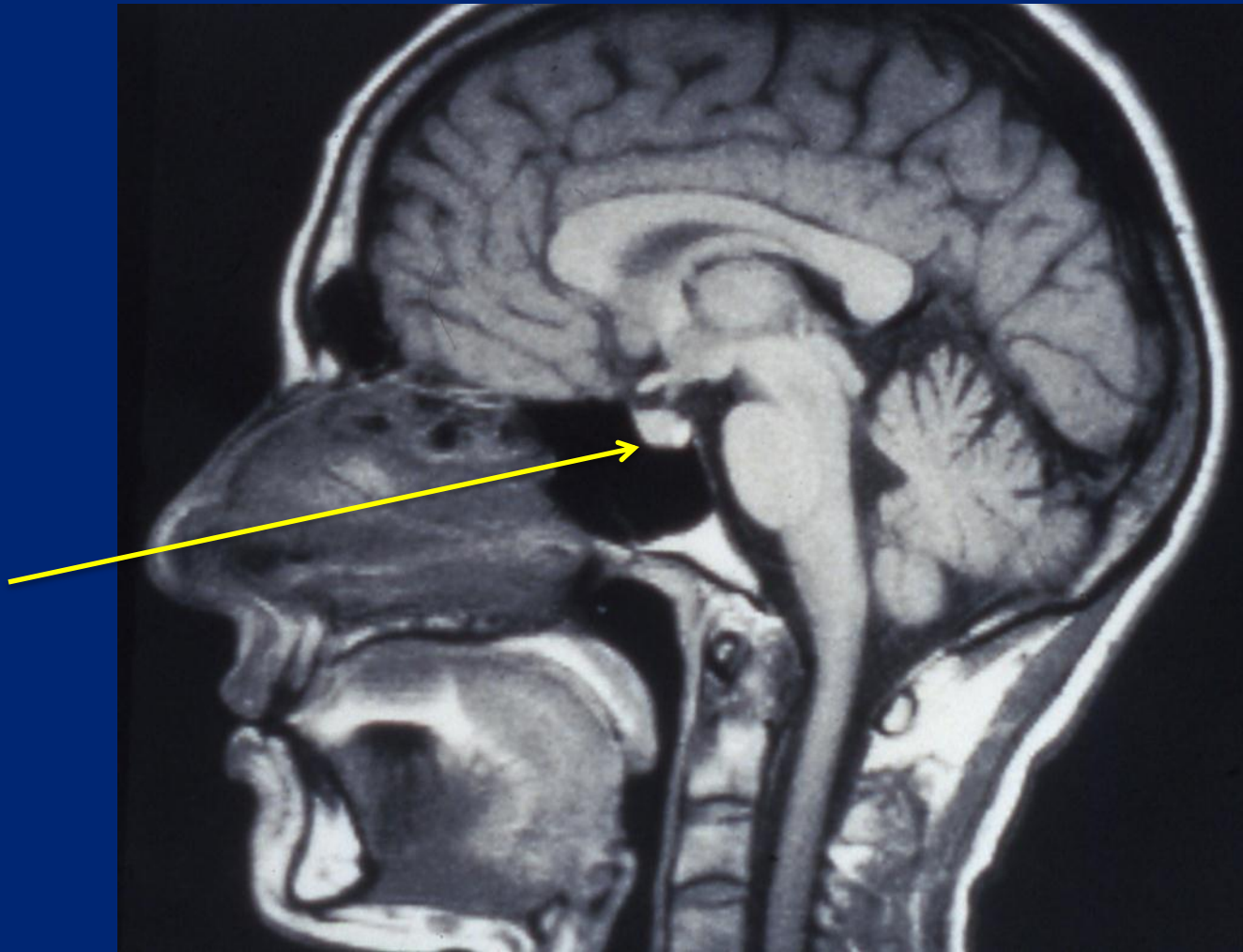
Correlation of Perceived, Sleep Disturbance & Fatigue with Motivation & Pituitary Hormonal Deficiencies in Patients with Pituitary Tumors

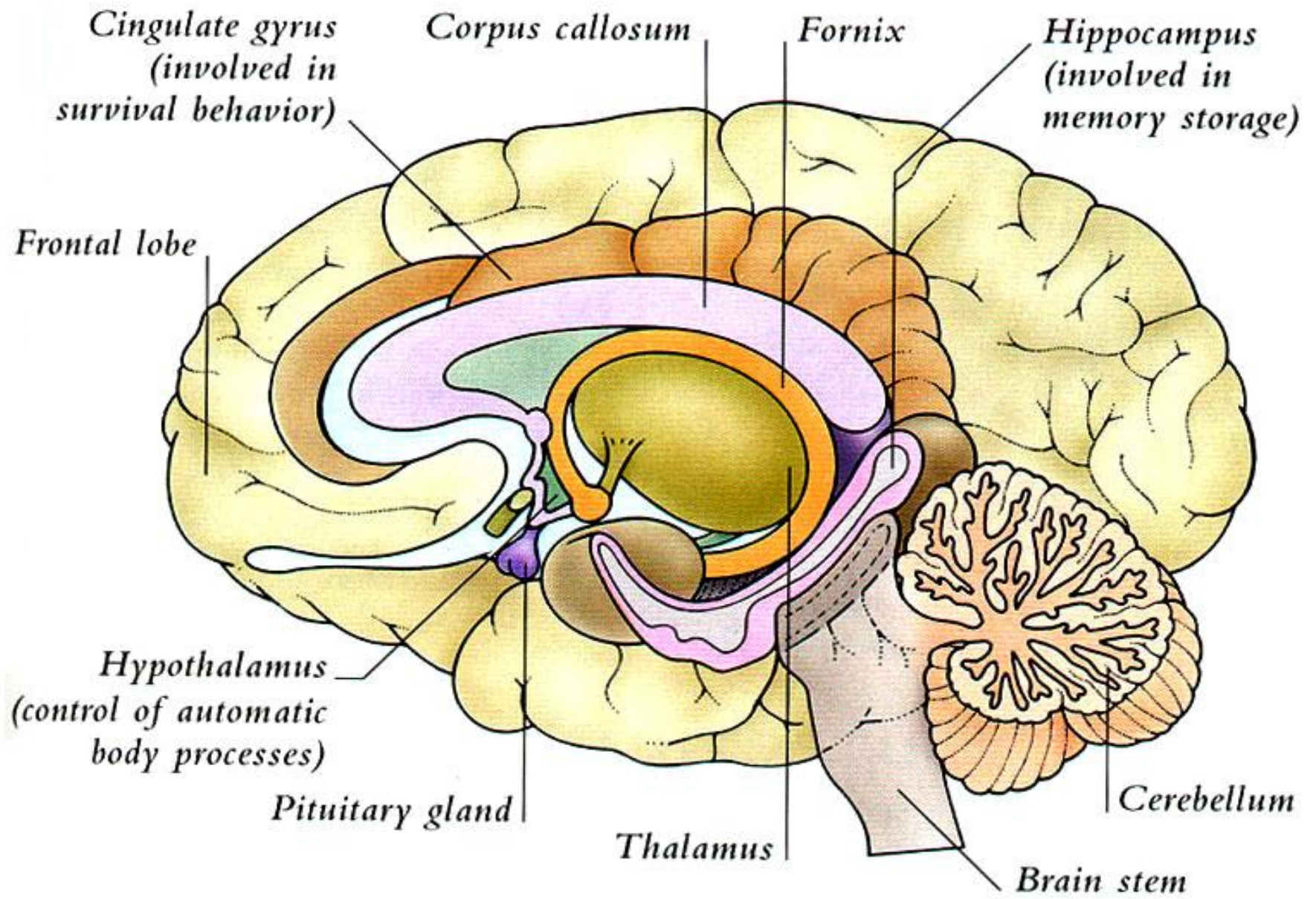
Chris Yedinak DNP,FNP, MN
Assistant Professor SOM

July 26th 2013

Background

Normal Pituitary Gland: sagittal section





Pituitary Adenomas

Classifications:

1. Size:

Microadenoma <1cm

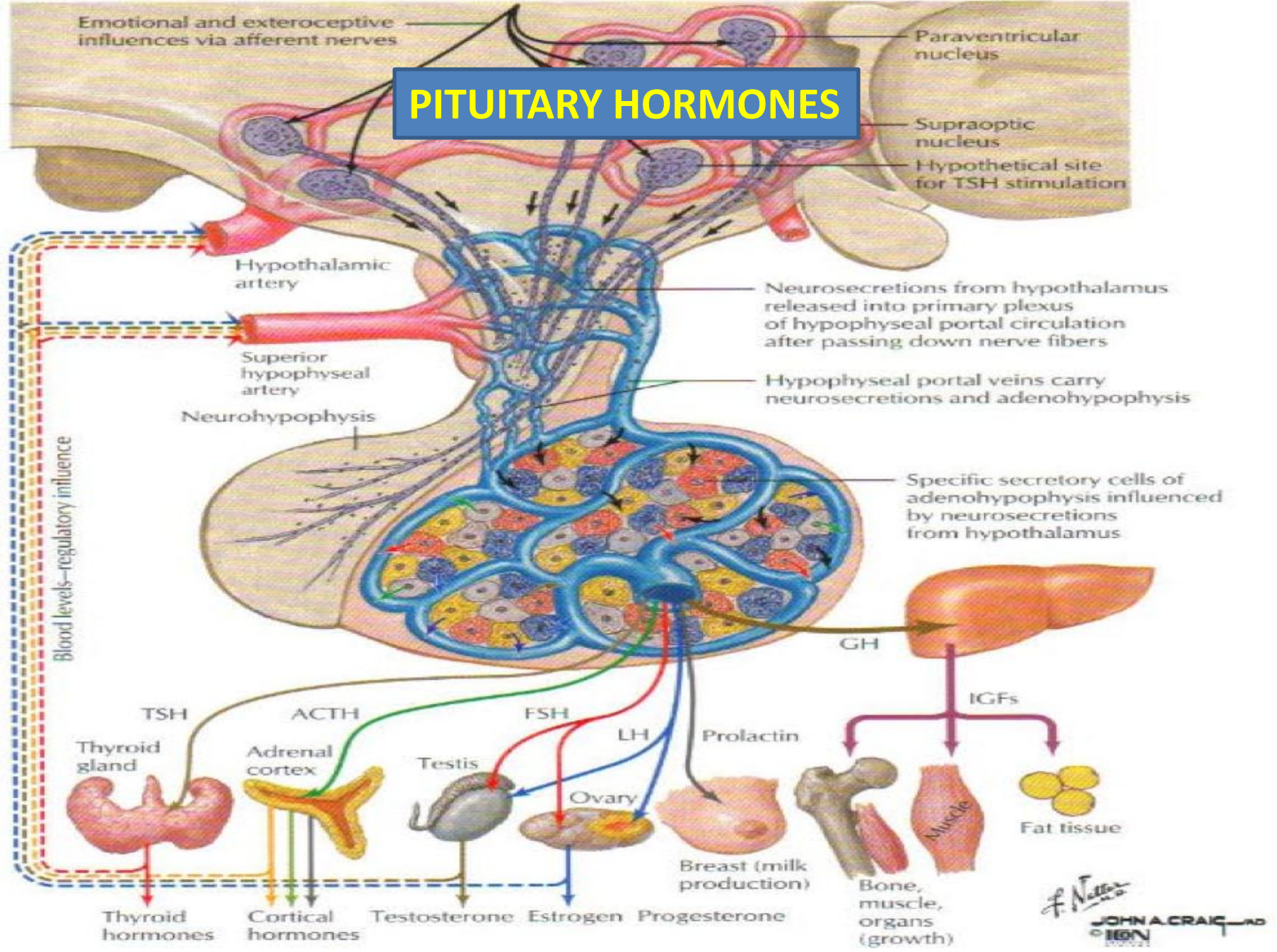
Macroadenoma >1cm

2. Hormonal Secretion:

Excess: Growth Hormone,
prolactin, ACTH/Cushing's

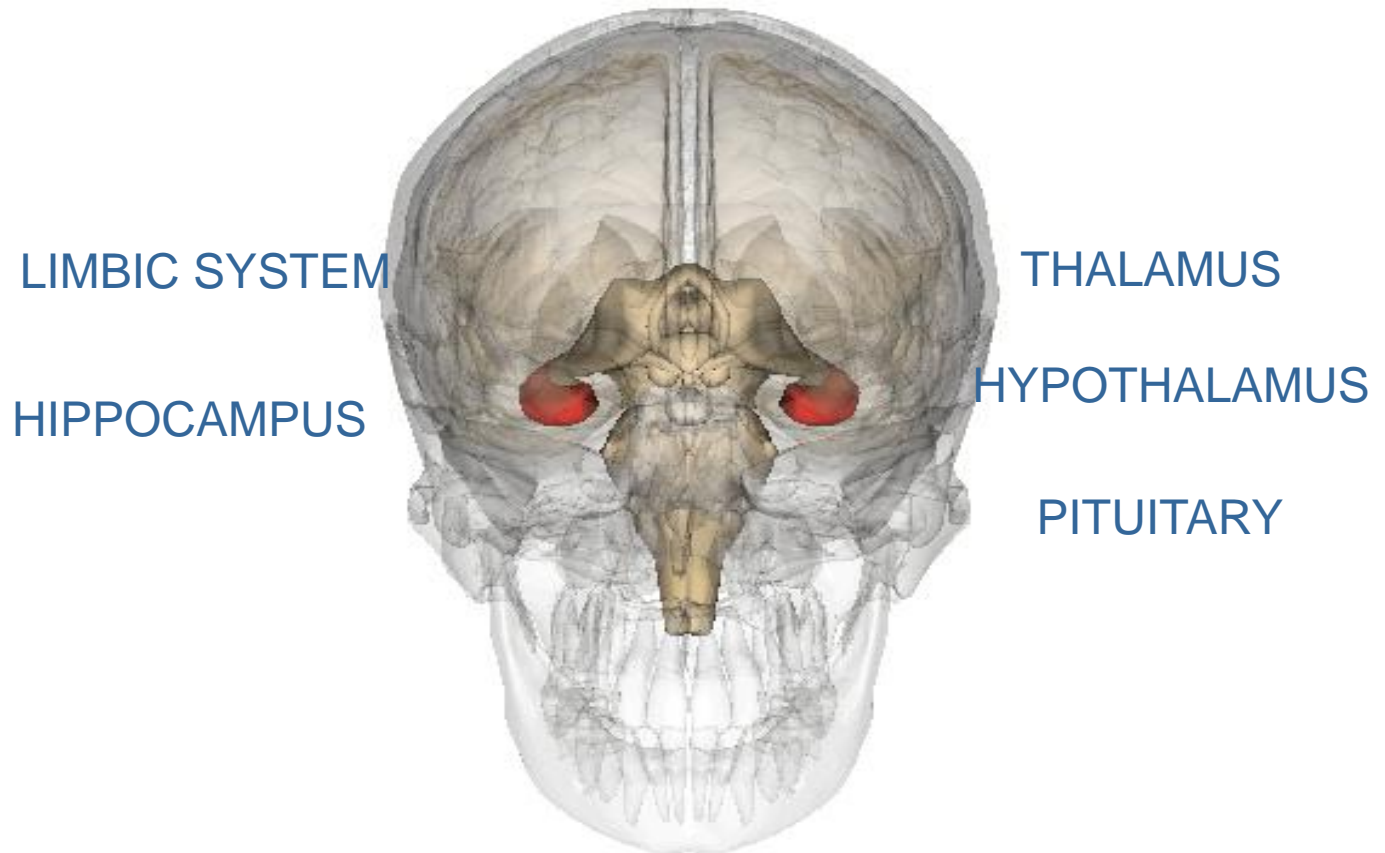
Deficiency: Any pituitary hormone

PITUITARY HORMONES



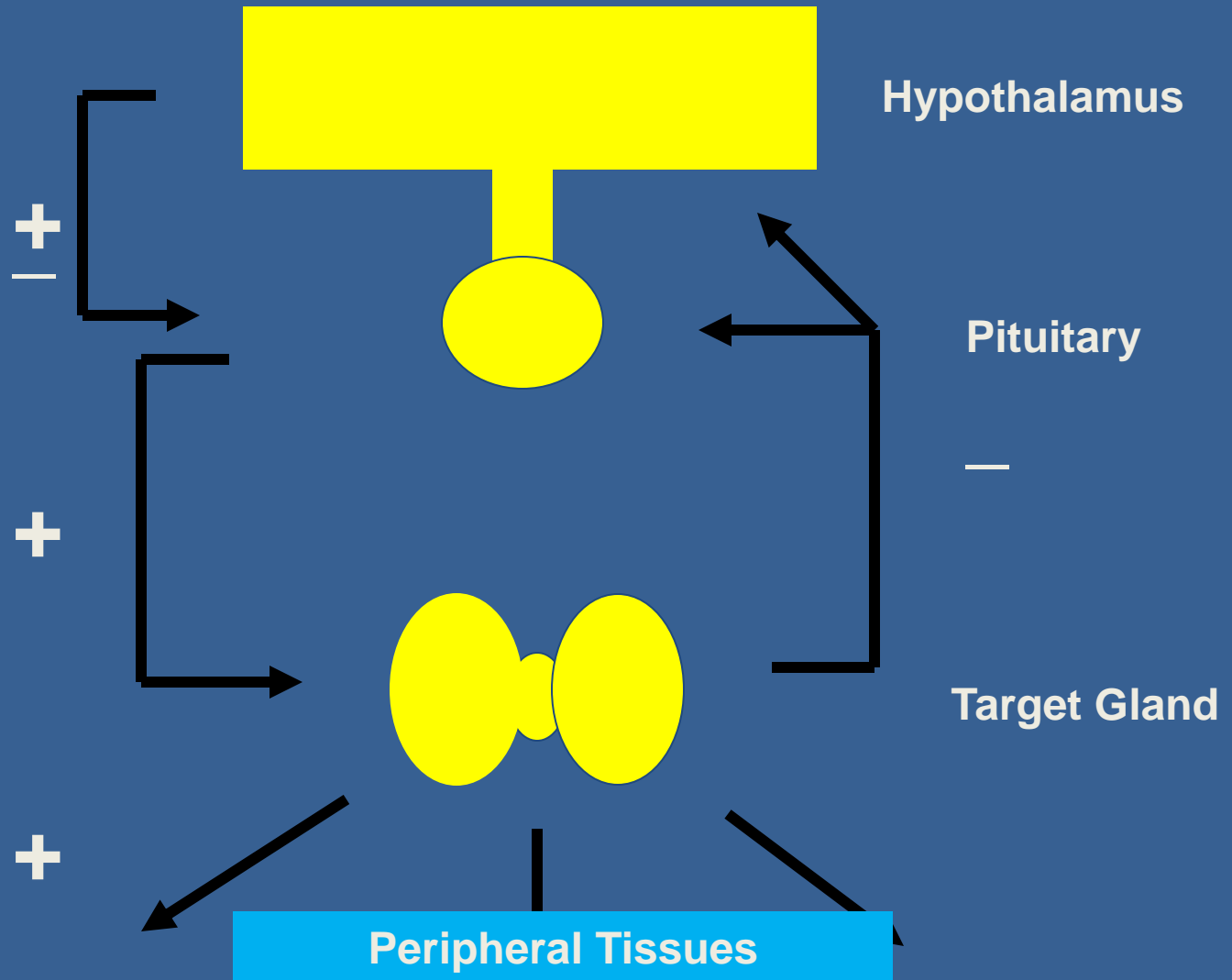
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JOHN A. CRAIG
© IGM

BRAIN STRUCTURES AND INFLUENCES



FEEDBACK LOOPS

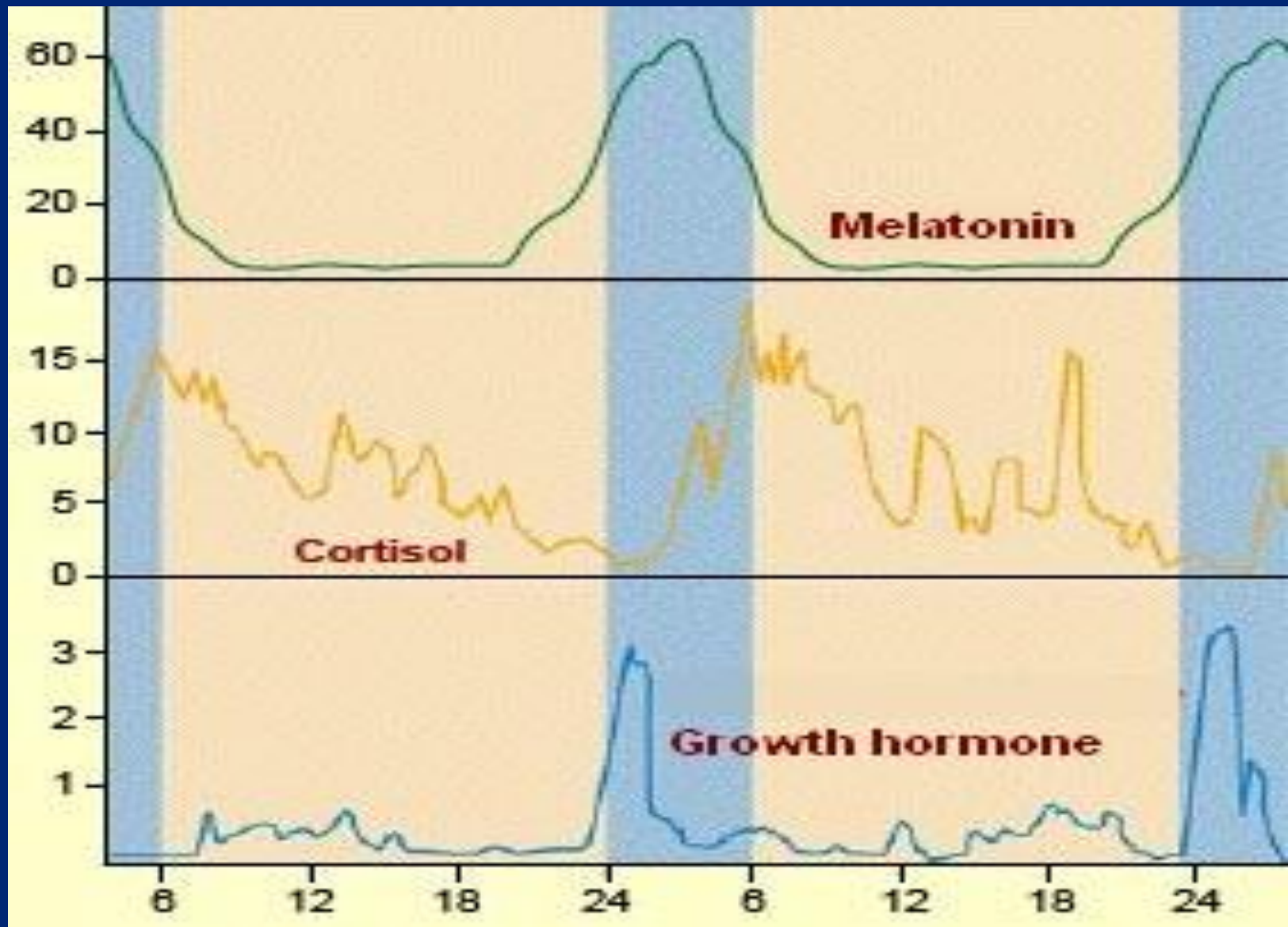
Outside World



Northwest Pituitary
Center

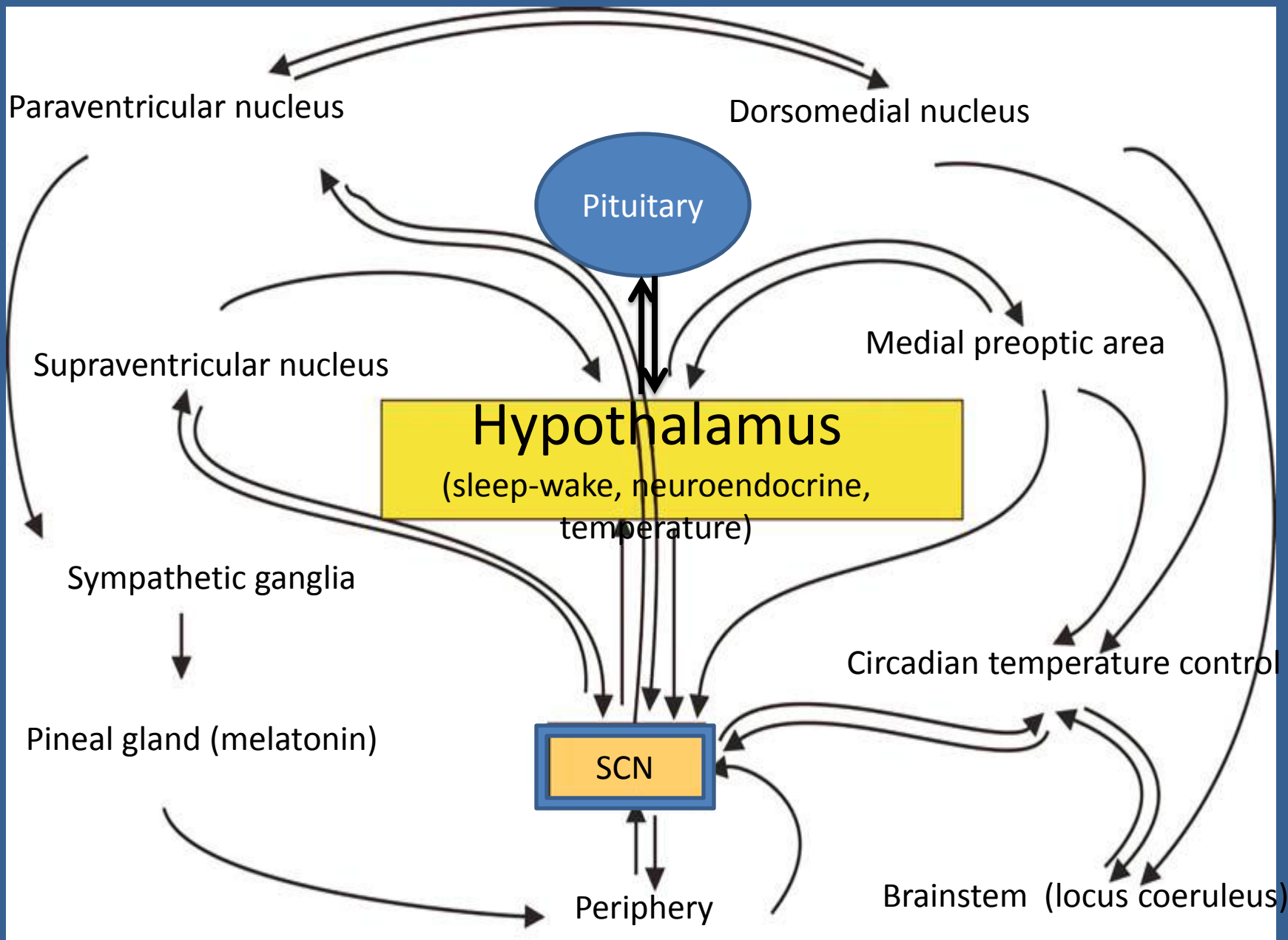
Oregon Health & Science University

Circadian Pituitary Hormone Production



Sleep Architecture

- Non- REM
 - 4 stages
 - theta waves
 - sporadic spindles and episodic rhythms from thalamus
 - 3 & 4 Slow wave sleep (SWS) with delta waves
- REM
 - motor activity is inhibited
 - most dreaming takes place
 - REM sleep deprivation disturbs normal body functions



Sleep Disruption

- Hormonal /biochemical disturbance
- Age & gender
- Mediators internal /external
- Disruption of clock gene expression
- Modulation of sleep phases such as SWS, delta activity or REM depletion

Hypothalamic Pituitary Adrenal (HPA) Axis & Sleep

- HPA axis is affected by sleep-wake cycles via direct and indirect effects of the circadian and homeostatic mechanisms
- Conversely, the HPA axis function has well documented effects on sleep wake cycles.

HPA Axis/Cortisol

1. Low AM salivary cortisol levels have been correlated with patient perception of poor sleep quality, frequent waking, insomnia and sense of non-restorative sleep.

- Backhaus. J., Junghanns K., Fritz Hohagen.F., (2004) Sleep disturbances are correlated with decreased morning awakening salivary cortisol *Psychoneuroendocrinology* 29, 1184–1191

2. Depression - associated with high levels of nocturnal hypothalamic activity & CRH over secretion & HPA axis stimulation have been associated with depression . Studies contradictory

Dienes.K.A.,Hazel.N.A., Hammen.C.L. (2012)Cortisol secretion in depressed, and at-risk adults.

Psychoneuroendocrinology (2013) 38, 927—940

Antonijevic I.A., Murck.H., Frieboes.R., Uhr.M., & Steiger.A. (2003) On the role of menopause for sleep-endocrine alterations associated with major depression. *Psychoneuroendocrinology* 28 (2003) 401–418

Cortisol

- When cortisol levels are elevated secondary to stressors, animal models have demonstrated resultant high melatonin levels- have a sedative effect during stress.


Guesdon.V., Malpoux.B.,Delagrange.P.,Spedding.M., Cornilleau.F., Chesneau.D.,Haller.J.,Chaillou. E.(2013). Rapid effects of melatonin on hormonal and behavioral stressful responses in ewes. *Psychoneuroendocrinology* (2013) 38, 1426—1434

Follicle Stimulating Hormone (FSH) & Lutenizing Hormone (LH)

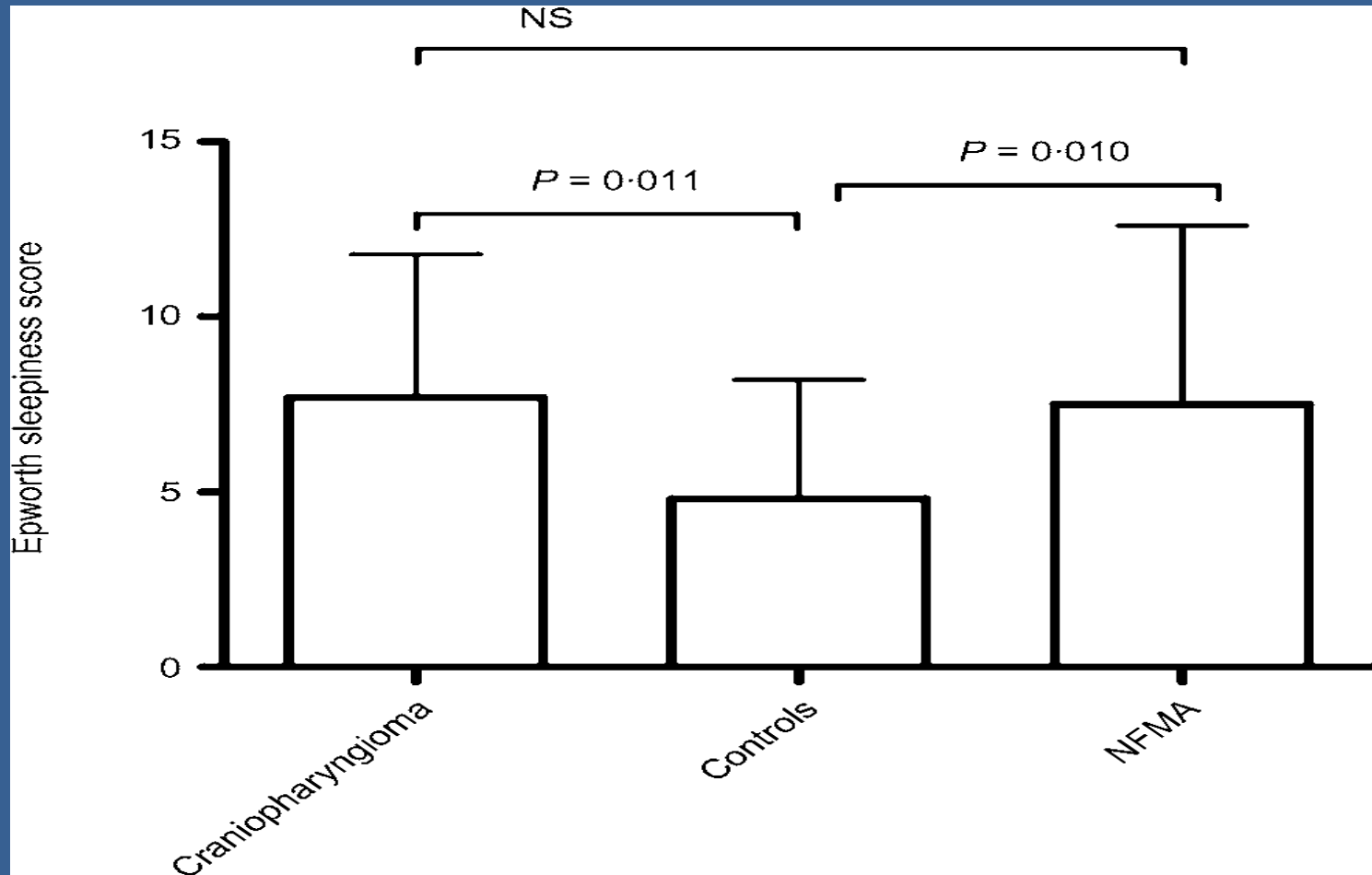
- Decreased SWS was noted in association with elevated FSH and LH levels in post menopausal woman with blunted FSH/LH response in depression.

Antonijevic I.A., Murck.H., Frieboes.R., Uhr.M., & Steiger.A. (2003) On the role of menopause for sleep-endocrine alterations associated with major depression. *Psychoneuroendocrinology* 28 (2003) 401–418

Growth Hormone (GH)

- Levels decrease with age
- Preferentially secreted during deep, slow-wave sleep (SWS) associated with  Ghrelin
- GH deficiency associated with decreased total sleep time and increased sleep fragmentation compared to controls
- GH Deficiency associated with decreased energy and fatigue
- Van Cauter.E., Latta.F., Nedeltcheva.A., Spiegel.K., Leproult.R., Vandenbril.C., Weiss.R., Mockel.J, Legros.J.J., Copinschi.G. (2004). Reciprocal interactions between the GH axis and sleep. *Growth Horm IGF Res.* Jun;14 Suppl A:S10-7.

Daytime Somnolence



Epworth sleepiness scores are increased in patients with craniopharyngioma healthy controls patients with NFMA

van der Klaauw, A.A., Biermasz, N.R., Pereira, A.M., van Kralingen, K.W., Dekkers, O.M., Rabe, K.F., Smit, J.W., Romijn, J.A. (2008) Patients cured from craniopharyngioma or nonfunctioning pituitary macroadenoma (NFMA) suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls. *Clinical Endocrinology (Oxf)*. Nov;69(5):769-74. doi: 10.1111/j.1365-2265.2008.03284.x. Epub 2008 Apr 24

Fatigue

- Defined in humans as self reported low levels of stress recovery associated with high allostatic stress load.
- Sleep deprivation = decreased time to task failure and cognitive performance and higher perceived exercise fatigue but no difference in muscle fatigue from non-deprived controls.

Temesi,J., Arnal,P.J., Davranche. K., Bonnefoy.R., Levy.P., Verges.S., & Millet,G.Y.(2013)Does Central Fatigue Explain Reduced Cycling after Complete Sleep Deprivation? *Medicine & Science in Sports & Exercise*, Publish Ahead of Print DOI: 10.1249/MSS.0b013e31829ce379

- Hypocretin-1 and melanin-concentrating hormone, measured in the human amygdala/hypothalamus shown to increase after eating and prior to sleep

Blouin.A.M., Fried.I.,Wilson.C.L., Staba.R.J.,Behnke.E.J., Lam.H.O.,Maidment.N.T., Karlsson.A.E., Lapierre.J.L & Siegel.J.M (2013). Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction.*Nature Communications*. DOI: 10.1038/ncomms2461

More Fatigue

- Animal models have demonstrated structural neuronal changes with sleep deprivation and central fatigue that were reversible with sleep. The impact of chronicity is unknown.

Chen,J.R.,Wang.T.J.,Huang.H.Y., Chen.L.J.,c Huang.Y.S.,Wang.Y. &Tseng.J.G.(2009).Fatigue Reversibly Reduced Cortical And Hippocampal Dendritic Spines Concurrent With Compromise Of MotorEndurance And Spatial Memory. *Neuroscience* 161 (2009) 1104–1113

Motivation

- Few studies have correlated sleep, fatigue and motivation
- 581 subject study of work stress -found a significant correlation between low AM cortisol levels, lack of energy , motivation ($r=0.11, p=0.036$)

EEK.F., Karlson.B., Garde.A.H.,Hansen.M.,& Ørbæk.P., (2012) Cortisol, sleep, and recovery — Some gender differences but no straight associations. *Psychoneuroendocrinology*. 37, 56—64

AIM

For patients with pituitary adenomas:

- Assess patient perception of severity of sleep disturbance and fatigue
- Evaluate the relationship among sleep disturbance, fatigue & motivational disturbance.
- Assess the relationship to tumor size (macro or micro- adenoma) and/or hormonal dysfunction

Study Design/Methods

- Prospective
- Cross-sectional
- Single site
- Convenience sample
- 17 item questionnaire
- Likert scale of severity dysfunction (6 pt)
- Questions adapted from:
 - Epworth Sleepiness Scale
 - Fatigue Severity Scale (Krupp 1989)
 - Eysenck Personality Inventory.

Questionnaire : Severity 0-6

Fatigue	my fatigued interferes with my work life
	I am fatigued during the day
	my fatigue disrupts my family life
	my exercise is limited by my fatigue
	I lack energy to do social activities with friends
Sleep	
	I wake early morning & can't go back to sleep
	I wake up tired
	I fall asleep when I sit quietly/read
	I sleep much of the day
	I have trouble getting to sleep
	I Wake frequently
Motivation	
	Others seem to get more done in a day than me
	I lack motivation to do things.
	I lack energy to do my household chores
	motivated if my work is acknowledged/
	I like seeing what I have accomplished myself
	I feel like getting things done around the house

Demographics

N=67

Female n=47

Male n=20

MeanAge/yrs	42.6	5
Mean # Hormonal Def	0.5	1
Micro <1cm	26(55%)	8(40%)
Macro >1cm	18(38%)	13(65%)
Medical Hx	12(25%)	7(35%)
Non-Functioning	19 (40%)	13(65%)
Hyper-Functioning	19 (40%)	3(15%)
other	9(20%)	4(20%)

Results: Spearman's Correlations

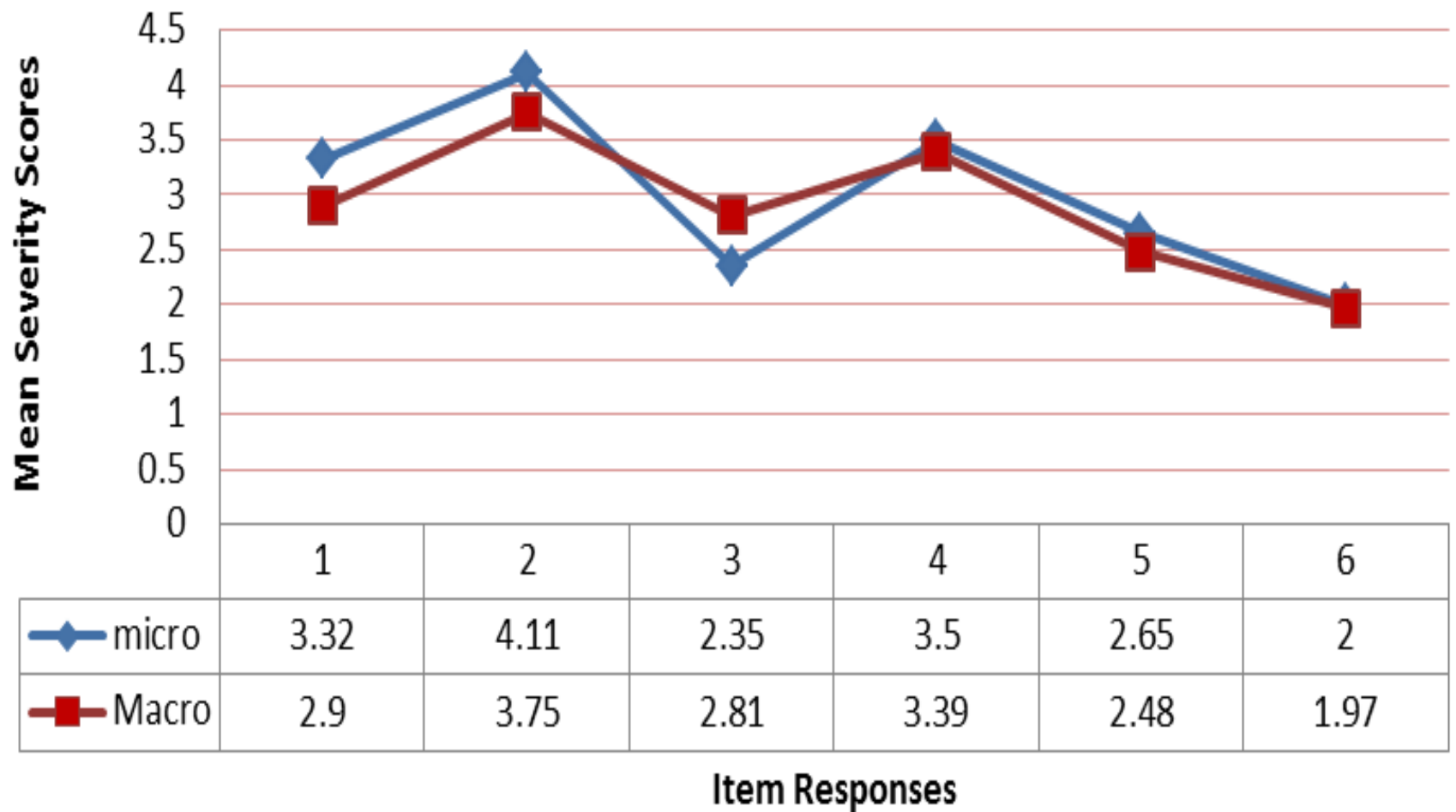
Categorical	Sleep	Fatigue	Motivation
	-	-	-
Age	-	-	-
Gender	-	<i>$r=-.29, p=.015$</i>	-
# deficiencies	<i>$r=-.35, p=.004$</i>	-	-
Size of Tumor	-	-	-
Med Hx	-	-	-
Diagnosis	-	<i>$r=-.29, p=.016$</i>	<i>$r=-.25, p=.04$</i>

Mean Severity Scores:

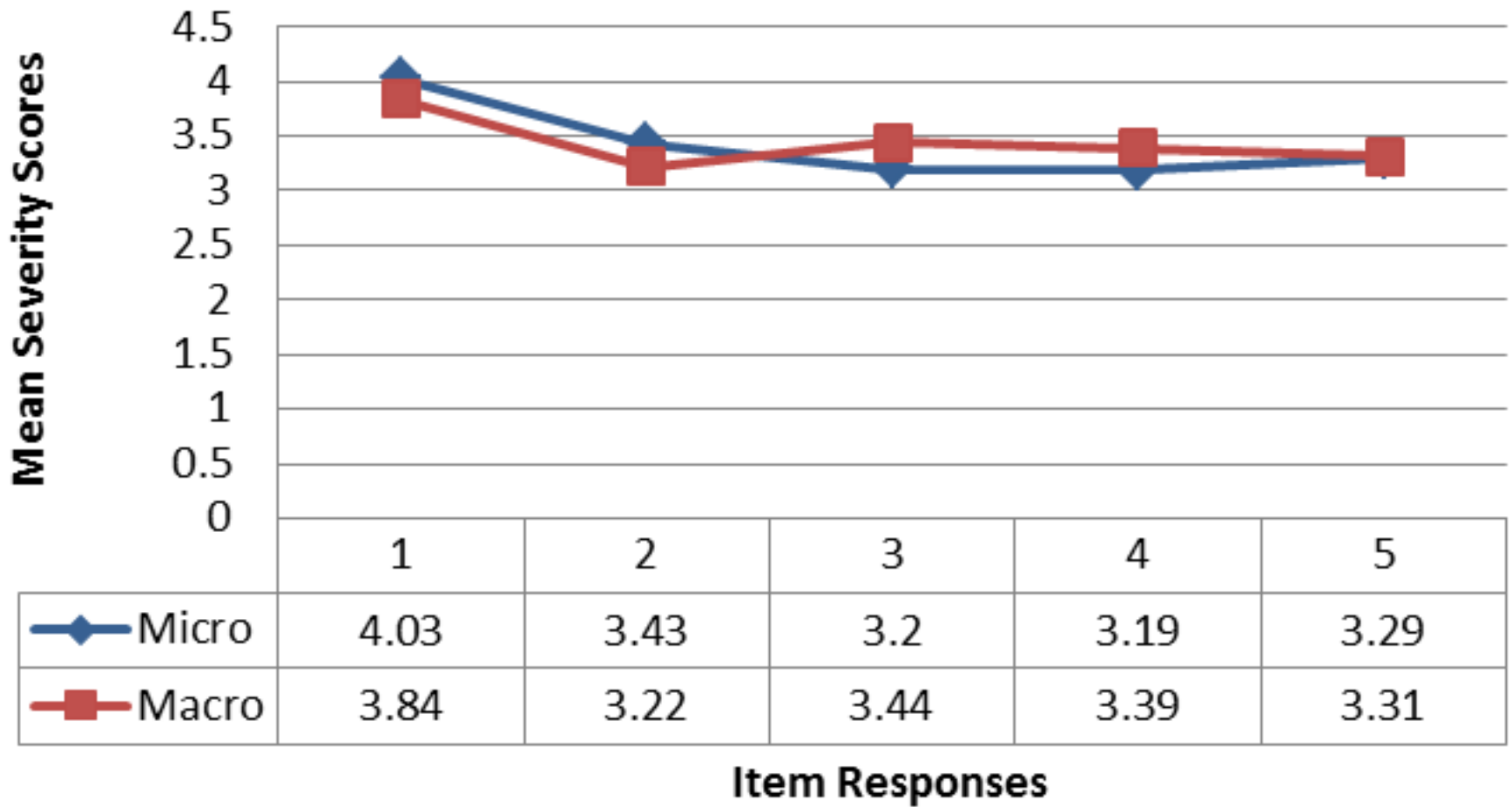
by

Dysfunction & Item

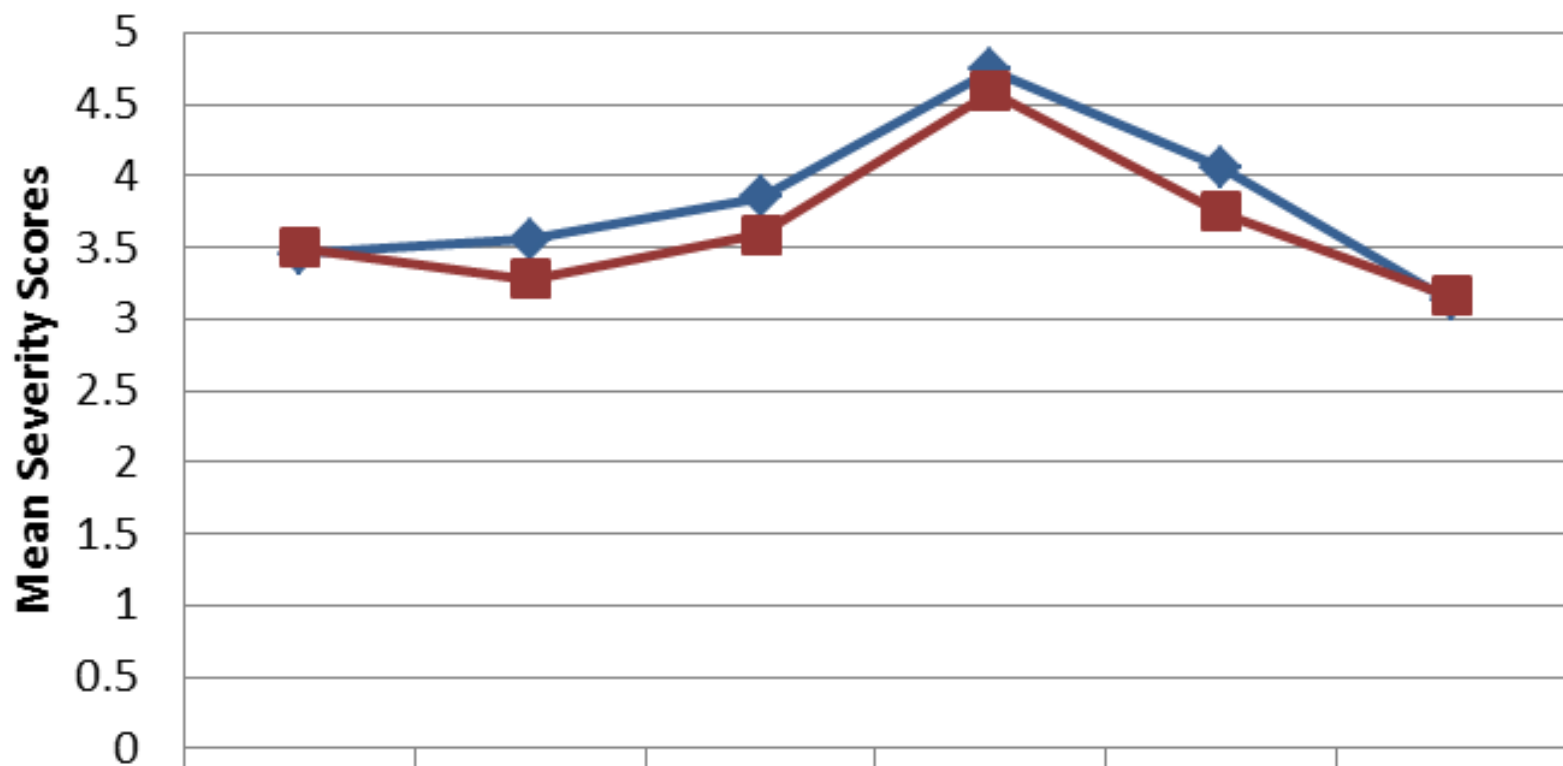
Sleep



Fatigue



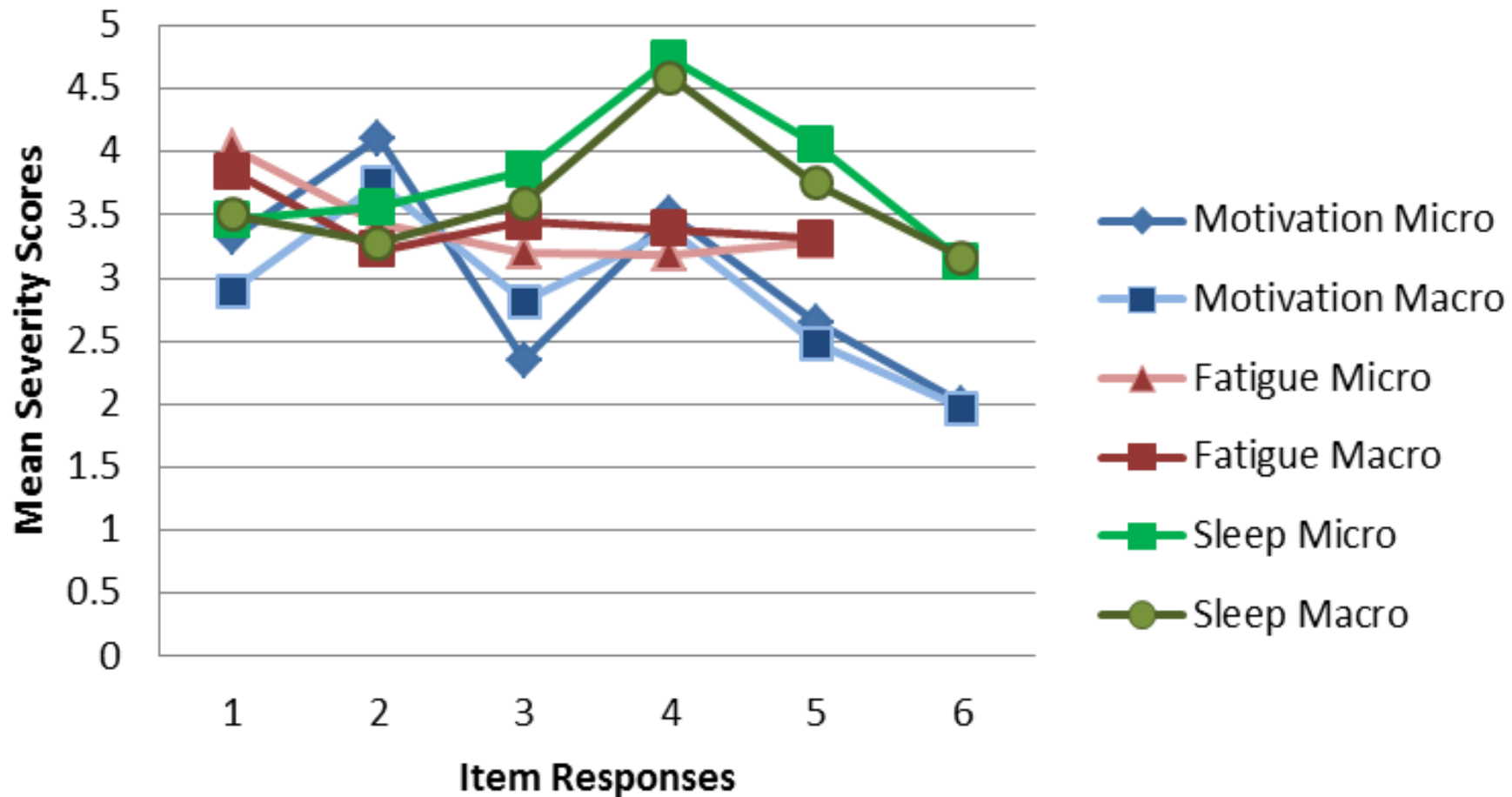
Motivation



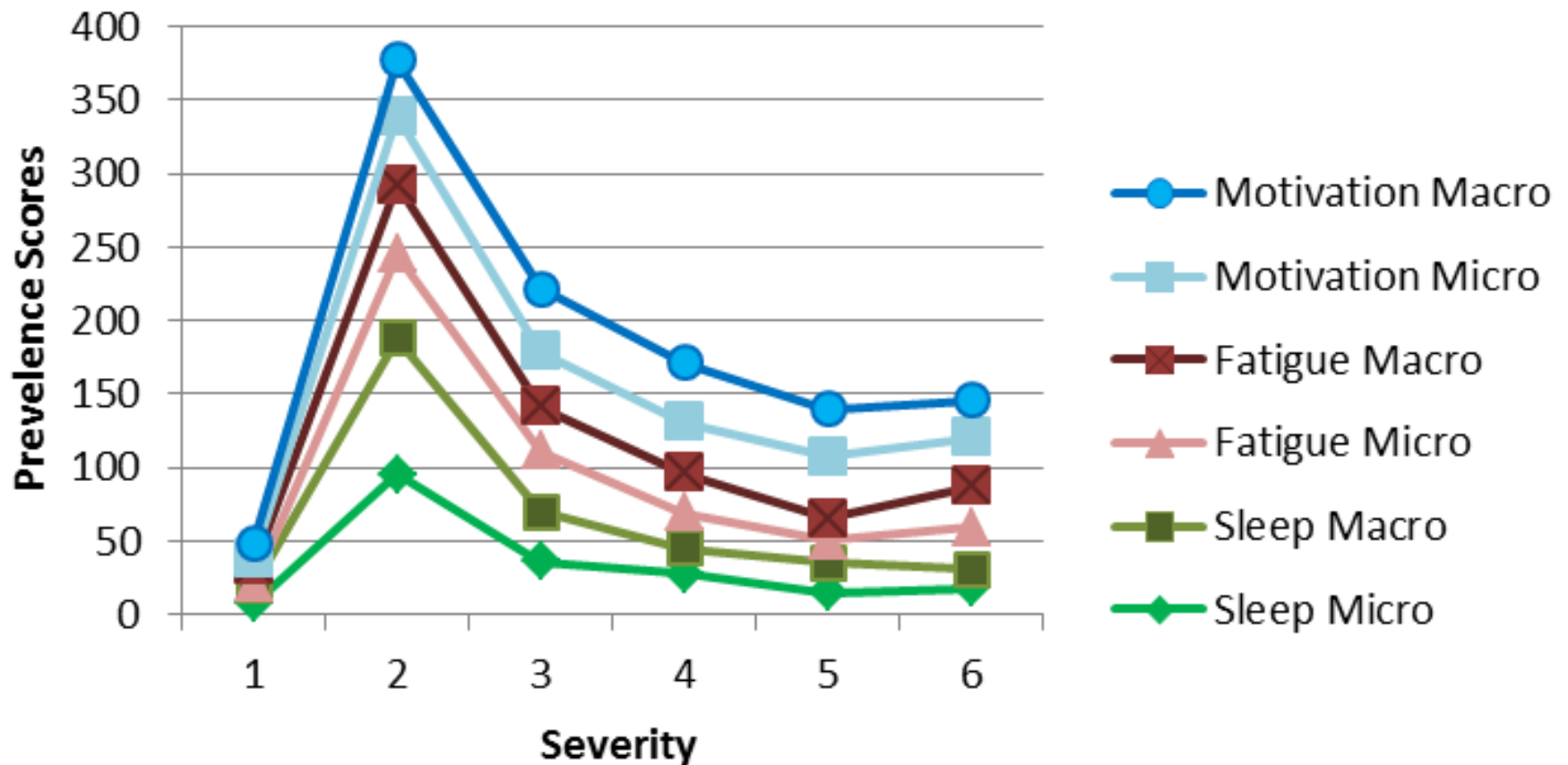
	1	2	3	4	5	6
◆ Micro	3.46	3.56	3.85	4.74	4.06	3.13
■ Macro	3.5	3.28	3.59	4.59	3.75	3.16

Item Responses

Relationship: Sleep, Fatigue, Motivation



Prevelence Pattern



Conclusions

- Patients with pituitary adenomas experience a moderate level of sleep dysfunction.
- All patients reported similar and moderate levels of sleep dysfunction, fatigue and motivational disturbances.
- Larger tumor size was consistently, but not significantly, associated with worse dysfunction in sleep, fatigue and motivation.
- Female gender was only significant for increased fatigue.
- Numerically, more hormonal deficiencies correlated with greater sleep dysfunction.
- HF tumors correlated with worse fatigue and motivation

Implications

- Treatment of sleep disturbance in patient's with PA is multifaceted .
- More research is needed with respect to sleep phase dysfunction in PA in order to focus treatment.
- Further evaluation with differentiation of PA hormonal hyper-secretion and specific deficiencies is indicated.

A scenic view of a city at sunset. In the foreground, a cable car is suspended from cables, moving across the frame. The city below is illuminated by the warm glow of the setting sun, with a large stadium and several high-rise buildings visible. The background features a range of mountains under a sky with soft, orange and blue hues.

Thank you.

Questions?

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