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Request for Promotion to Professor
ACADEMIC FACULTY

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PERSONAL SUMMARY OF CONTRIBUTIONS TO MERCER UNIVERSITY SCHOOL OF MEDICINE

As an Associate Professor in the Department of Biomedical Sciences, my primary responsibility has been in research, with secondary responsibilities in teaching and service. This summary and application for promotion to Professor describes my accomplishments in these areas.

In the 10 years that I have served as a faculty member at MUSM, I believe I have exhibited exemplary performance in research, teaching and service and have demonstrated continued success and development in these areas. It has been a privilege to work in the MUSM academic environment, and I hope that my accomplishments, as outlined below, along with my strong sense of responsibility and my efforts in collegiality will be considered as befitting of continued service to the School and the University.

Research/Scholarly Activity

Ten years ago, I joined the faculty of MUSM immediately after completing a post-doctoral fellowship at the University of Utah. In those ten years, I have fully developed my research program by designing and implementing several new and exciting projects that will increase our understanding of the neural systems that underlie addiction. I have demonstrated continued excellence in the field of addiction research since being promoted to Associate Professor in 2012, as I have published six papers (with two more in currently in preparation) in highly regarded and internationally recognized journals, presented data at nine national/international meetings, written two textbook chapters, been invited to give seminars at other universities, reviewed grants for national and international granting agencies, trained numerous undergraduate and graduate students, peer reviewed manuscripts for national/international journals, have had NIH funding, and will likely receive funding for a new project from the NIH early next year. Together, these data support an evaluation of sustained excellence in research and the achievement of notable expertise in my field. My research is clearly well regarded by my peers as evidenced by my procurement of extramural research support, and the continued publication and oral presentation of my data in national and international venues. In summary, maintaining a successful research program, coupled with continuous publishing, funding and presentation of my data, indicate that I have demonstrated sustained excellence in research and scholarly activity.

Teaching

In the MUSM Biomedical Problems Program curriculum (which ended in the spring of 2017), I have tutored and served as the pharmacology discipline representative for 9 years in Brain and Behavior and 10 years in Neurology, while serving as the pharmacology discipline representative for Hematology, which has allowed me to develop interdisciplinary teaching proficiency. In 2015, I took responsibility for giving resource sessions on material that was previously taught by the neuroscience faculty, and oversaw a portion of the neuroanatomy wet lab instructional sessions. My tutor evaluations from students have been consistently very positive, and according to these evaluations, I managed tutorials in a professional manner and have provided students with a constructive learning environment. In the new curriculum (which started in the fall of 2016), I taught in all four modules of Block 2 and continued to teach neuroanatomy in the wet lab. I was also responsible for the development of all of the curricular material for Module 2 of Block, including organizing team-based learning sessions. My evaluations by students in Block 2 continue to be very positive. Together these data showing my continued participation and development of the medical school curriculum, along with my very positive tutor evaluations, indicate that I have demonstrated sustained excellence in teaching.

Service

At MUSM I have served on committees and participated in activities that promote collegiality, curricular development, and/or research. I served on the MUSM Curriculum and Instruction Committee until 2014, where I strived to represent the interests of the Division of Basic Medical Sciences (now the Department of Biomedical Sciences). I have recently been elected to the Promotion and Tenure committee for MUSM, and was called to serve on the University Strategic

Planning Committee for Goal 2 of Mercer University's Strategic Plan in May of 2017. I am also currently the chair of the Neuroscience faculty search committee for MUSM. I also have served as a pre-clinical advisor for 13 medical students, and have mentored 3 Masters of Biomedical Science graduate students. I have also been involved in service on the national and international levels. I have served as an ad-hoc member of the Neurobiology of Motivated Behavior study section at the National Institutes of Health Center for Scientific Review, reviewed grant applications for the Austrian Science Fund, participated in the development of the David Lehr award for the American Society for Pharmacology and Experimental Therapeutics and served as a manuscript reviewer for several national and international journals. Together, these data show that I have demonstrated sustained excellence in service at the medical school, university, national and International levels.

In summary, in the five years since I was promoted to Associate Professor, I have demonstrated that I continue to be an exemplary member of the faculty by maintaining an active research program that has been funded by the NIH, providing outstanding teaching to the School of Medicine, and continued service at the university, local, national and international levels. I plan to remain engaged in research, teaching, and service at this level until I retire from MUSM.

I sincerely appreciate the time of fellow faculty in the Department of Biomedical Sciences and the MUSM Promotion and Tenure Committee in the review and consideration of my application.

LIST OF REFEREES

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NOT NECESSARY TO INCLUDE REFERENCES IN APPLICATION. REVIEWERS WILL SEE LETTERS

DOCUMENTATION OF RESEARCH/SCHOLARSHIP/CREATIVE ENDEAVORS

I. Philosophy and Goals of Research/Scholarly Activity

My philosophy is that research helps to provide a fulfilling academic environment for me, my colleagues and my students. My research goals are the same as they were on my first day of graduate school: to design and perform studies to reveal novel pathways involved in addiction; to be engaged and to engage others in innovative neuroscience research; to consistently publish my work in high-quality journals, and to secure and maintain extramural funding. While these basic goals have remained the same, I have also developed significantly as a researcher in my time at MUSM. I am more focused on my line of research (which involves investigating the neural pathways that are involved in habitual drug abuse), I'm less afraid to take risks, I am more eager to take on challenging research projects that address difficult and unanswered questions and I am more willing to learn and utilize techniques that are outside of my area of expertise or to seek out collaborators that can provide support in techniques in which I am unfamiliar. I feel that I have been successful in these endeavors, as I have published and presented a number of research papers and posters, have secured funding from the NIH and have trained several undergraduate and graduate students. I also have gained national and international recognition for my research and expertise, as my abstract was accepted for presentation at the 2013 International Basal Ganglia meeting, and I have been asked to write book chapters in the *Handbook of Basal Ganglia Structure and Function* and *Fluoxetine: Pharmacology, Mechanisms of Action and Side Effects*.

I also believe that by maintaining an active research program, I can provide students with research experiences, keep my knowledge of scientific advancements current in order to best train our medical students, and collaborate with other faculty to benefit the collective research effort at MUSM. I value both internal collaborations with MUSM faculty and new opportunities to collaborate with researchers outside of MUSM. Quality research comes from the sharing of ideas in a constructive environment, which we have and should strive to maintain at MUSM. Scientific advancements benefitting medicine require thoughtful research approach and implementation from the smallest molecular detail up to the level of administering treatments to patients. While my future research will likely remain focused on the neurochemical and behavioral changes induced by psychostimulant treatment, as well as the interactions between these two parameters, my findings will provide a greater understanding of the neural mechanisms that contribute to the deleterious effects of drug abuse.

II. Underlying Themes of Research and Future Directions

A. The Role of the Patch-Matrix System in Habitual Drug Abuse

The primary focus of my research program is to obtain knowledge of the neural systems involved in habitual drug abuse, as a greater understanding of these systems are necessary to improve our ability to treat addiction. The majority of the research studies that have taken place in my laboratory over the past decade have involved examination of role of the patch-matrix system in the behavioral effects of psychostimulants. Our laboratory, as well as the laboratories of others have shown that the patch-matrix system of the striatum is involved in persistent, inflexible behaviors, such as psychostimulant-induced stereotypy. Stereotypy consists of focused, repetitive movements that coupled with an inability to initiate appropriate responses to external stimuli. Because habitual drug abuse is often persistent and inflexible, it is possible that addiction is also mediated by the patch-matrix system. Psychostimulant-

induced stereotypy, such as that induced by methamphetamine is due to enhanced activation of the patch system, which facilitates internally-cued urges, relative to the matrix system, which mediates adaptive behavioral responses. We have shown that ablation of patch system neurons decreased METH-induced stereotypy by reducing the imbalance in activity between the patch and matrix compartments (see **Major Accomplishments/Contributions in Scholarship, Sections A and B**). It is not known, however, whether an imbalance in the patch-matrix systems underlies addiction or habitual behaviors. The long-term goal of our research is to elucidate the neural pathways that underlie addictive behaviors to reveal novel therapeutic targets for treating addiction. Our short-term goal is to determine the contribution of the patch-matrix system to reward processes and habitual behaviors. Our *central hypothesis* is that methamphetamine-mediated reward and habitual use are due to predominant activation of the patch versus matrix system, which occurs due to the strengthening of synaptic connections in patch-based circuits and/or the weakening of synaptic connections in matrix-based circuits. This hypothesis is supported by our previous work and the work of others, showing gene expression is increased in the patch and diminished in the matrix following repeated exposure to psychostimulants, as well as our studies showing that patch-based circuits are necessary for habit formation (see **Major Accomplishments/Contributions in Scholarship, Section A**). The patch system may also facilitate reward processes, as animals will self-stimulate if an electrode is placed in the patch region of striatum. Our own data indicates that methamphetamine reward is attenuated when the predominant activation of the patch system is reduced (see **Major Accomplishments/Contributions in Scholarship, Sections A and B**). A major goal of our research is determine if habitual and drug-seeking behaviors are the result of an imbalance in the patch-matrix systems and whether long-term changes in synaptic plasticity underlie this imbalance. We will accomplish these goals by exposing animals to methamphetamine-induced conditioned place preference (which is an index of drug reward) or habitual methamphetamine self-administration and then examining changes in synaptic plasticity in the patch vs. matrix compartments, to determine if these treatments alter the balance in activity between these two compartments. In a subset of animals, we will specifically lesion the patch compartment, to determine whether a loss of these neurons will attenuate methamphetamine-mediated reward and habitual use.

The project described above is the primary focus of our research and will provide the foundation for our future studies. This current line of research is based on data obtained during a previous AREA R15 award, which ended in February 2014 (see **Funded Grants**, below). When that R15 grant ended, a renewal application and a revision of the renewal application were submitted, but both proposals were not funded (see **Grants submitted, but not funded**, below). However, we made some modifications to our project and submitted this proposal as a new AREA R15 in February 2017. In July, we received a score (38) for this proposal, along with favorable reviews (see **Pending Grants**). We are in the process in revising this application for resubmission in October, and based on the comments we received, we are confident that this revised proposal will be funded.

B. The Role of the Patch-Matrix System in Tourette's Syndrome

We are also in the process of pursuing a new line of research that is related to our patch-matrix studies involving inflexible behaviors. Repetitive and inflexible behaviors are also seen in the context of psychiatric disorders, such as Tourette syndrome. Tourette syndrome is characterized by involuntary motor contractions and repetitive movements and that are thought to be fixed and inflexible in nature. Since patch-based neurons contribute to inflexible behaviors, it is possible that the inflexible motor tics observed with Tourette's syndrome are also due enhanced activation of the neurons of the patch compartment. We are currently in the process of performing exploring this hypothesis, by specifically

lesioning the neurons of the patch compartment prior to treatment with the serotonin agonist, DOI. DOI treatment induces involuntary head twitch responses in rodents, and is considered to be an animal model of Tourette syndrome. We predict that prior destruction of patch-based neurons will reduce DOI-induced head twitch responses. Since Tourette syndrome and obsessive-compulsive disorder share behavioral symptoms, we will also expand these studies to explore the role of patch-based neurons in marble-burying behavior, which is an animal model of obsessive-compulsive disorder. These additional studies are supported by a Navicent Health Foundation award (see **Funded Grants**, below), and will provide us with preliminary data for future NIH grant applications.

III. Unfunded Projects: Describe any unfunded projects to which you are devoting substantial time.

A. Reversal of psychostimulant withdrawal-induced symptoms of depression with ketamine

Abusers of psychostimulants report symptoms similar to major depressive disorder (MDD) after excessive drug intake followed by abstinence. It is thought that the MDD-like symptoms experienced during psychostimulant withdrawal may contribute to relapse and maintenance of addiction. Depletions in brain-derived neurotrophic factor (BDNF) in the limbic system (which mediates motivation, reward and emotional behaviors) are thought to underlie MDD. Given that MDD and psychostimulant withdrawal share symptomology, we hypothesized that diminished BDNF in the limbic system may also mediate depressive symptoms during withdrawal. Our laboratory was among the first to demonstrate that levels of BDNF in the limbic system were diminished following d-amphetamine withdrawal. Recent studies had indicated that the N-methyl-D-aspartate glutamate receptor antagonist, ketamine was effective in returning BDNF levels to control levels in animal models of MDD. We found that treatment with ketamine during the withdrawal period restored BDNF in the limbic system, particularly in the hippocampus, which plays an important role in emotional memory. Our studies revealed a neurochemical deficit that may underlie depressive-like symptoms during psychostimulant withdrawal and we were among the first identify BDNF as a target for pharmacological intervention to prevent relapse into drug-seeking behaviors (see **Major Accomplishments/Contributions in Scholarship, Section C).** The next step in this line of research was to confirm that ketamine treatment during withdrawal would prevent depression-like symptoms concomitant with the restoration of BDNF levels, using the forced swim test, which is a standard test for assessing depression in laboratory animals. However, stressors within our animal care facility prevented us from performing these behavioral tests. Fortunately, these issues with the animal care facility have been corrected, and we are in the process of resuming these behavioral studies. We hope to collect additional preliminary data over the next year to use for in a grant application to the Brain and Behavior foundation.

B. Mechanisms of methamphetamine-induced neurotoxicity

Repeated exposure to high doses of methamphetamine result in long-term neurotoxic damage to the dopamine (DA) neurons in the substantia nigra pars compacta (SNpc). There are the same neurons that are affected in Parkinson's disease, and recent studies indicate that those who chronically abuse methamphetamine are up to twice as likely to develop Parkinson's disease in their lifetime. Reactive oxygen species (ROS) are generated by methamphetamine and a common product of ROS-mediated oxidation of neuronal membranes is the reactive aldehyde *malondialdehyde (MDA)*, which can modify amino groups in proteins. Our laboratory utilized an antibody with specificity for MDA-bound proteins to detect the presence of MDA in METH-treated tissue we found that that multiple, high doses of

methamphetamine results in a significant increase in MDA-bound proteins in the SNpc (Horner, et al., 2011). A likely protein target of MDA is the mitochondrial enzyme ALDH-2, which is the primary enzyme responsible for the breakdown of DA. DA is metabolized by monoamine oxidase (MAO) to produce 3,4-dihydroxyphenylacetylaldehyde (DOPAL), which is oxidized by ALDH-2 to produce 3,4-dihydroxyphenylacetic acid (DOPAC). MDA can irreversibly inhibit ALDH-2 via adduct formation, leading to an accumulation of DOPAL, which is highly toxic to dopaminergic neurons. We hypothesized that chronic methamphetamine treatment increases MDA generation, which inactivates ALDH-2 and results in the accumulation of DOPAL, leading to the destruction of dopamine neurons via mitochondrial disruption (**Figure 1**). We designed several experiments, in conjunction with my collaborator, Dr. Jonathan Doorn, at the University of Iowa, to explore our hypothesis and generate preliminary data for an NIH grant application, with support from a MEDCEN award (see **Funded Grants**, below). Our initial studies indicated that following repeated methamphetamine treatment, ALDH-2 mRNA levels were increased in the SNpc, indicating that ALDH-2 synthesis may be up-regulated to compensate for the loss of functional ALDH-2 (**Figure 2**). Furthermore, our preliminary data suggested that levels of DOPAL were increased in the SNpc following repeated methamphetamine treatment (**Figure 3**). We were confident that our project was innovative and novel, as a link between DOPAL accumulation and methamphetamine-induced neurotoxicity had not been investigated. We submitted an R15 AREA application to support this project, and this proposal was not funded. We then added additional preliminary data gained as a result of our MEDCEN grant, and re-applied for funding, this time as an R03 pilot study grant. The initial R03 submission was scored; however, our resubmitted application received a score that was higher (i.e., worse) than the original submission. At this point, my collaborator and I decided to temporarily suspend these studies, with the intent to continue them at some point in the future. A

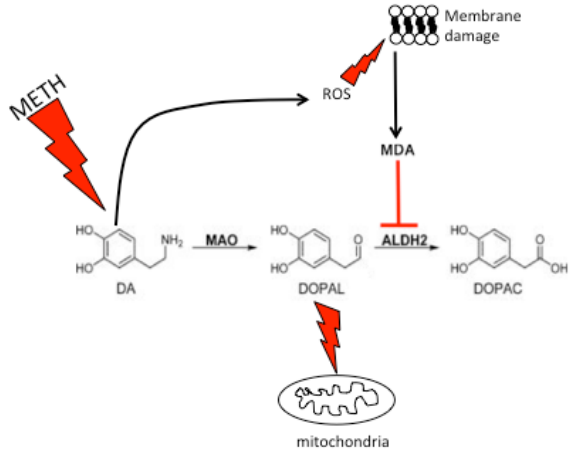


Figure 1. DA metabolism resulting in the formation of DOPAL. ALDH-2 is responsible for the conversion of DOPAL to DOPAC, and is found in high concentrations in the dopamine neurons of the SNpc. MDA, which is formed via METH-induced, ROS-mediated membrane damage, can irreversibly inhibit ALDH-2 resulting in the accumulation of DOPAL. DOPAL can exacerbate neuronal damage through the disruption of mitochondrial function (*adapted from Jinsmaa et al., 2009*). Lightning bolts indicate damage.

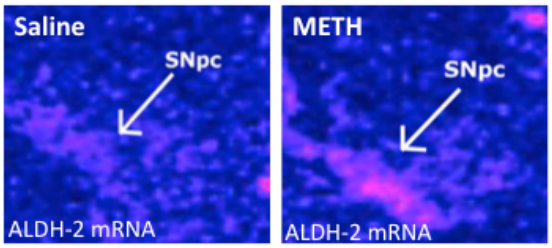


Figure 2. Treatment with repeated METH increased ALDH-2 mRNA expression in the dopamine neurons of the substantia nigra pars compacta (SNpc).

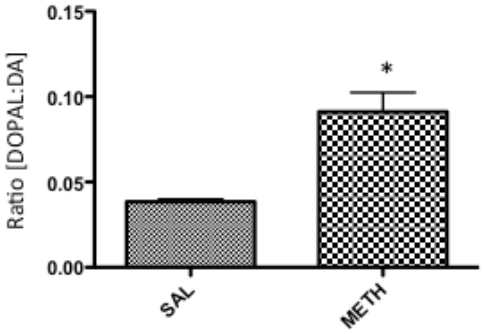


Figure 3. Repeated METH treatment results in the accumulation of the toxic metabolite DOPAL (expressed as the ratio of concentration of DOPAL to dopamine), suggesting that ALDH-2 function is impaired.

portion of these data were presented in poster form at the Society for Neuroscience meeting in 2014, and we are in the process of preparing a brief communication detailing our findings in ALDH-2 expression following repeated methamphetamine treatment, to be submitted as a brief communication to the journal *Brain Research* in December 2017.

Data from this project was presented at the annual Society for Neuroscience meeting:
Ryan C. Murray, Kevin A. Jiles*, Jonathan A. Doorn and **Kristen Ashley Horner**. Aldehyde dehydrogenase-2 expression is altered in the nigrostriatal system following a neurotoxic regimen of methamphetamine. Presented at the Society for Neuroscience Annual Meeting, San Diego, CA, November 9-13, 2013. **denotes undergraduate student co-author*

I was also invited to give a seminar at the University of Iowa College of Pharmacy where I presented our initial findings:
Cause or Effect? Reactive Aldehydes and Methamphetamine-Induced Neurotoxicity, given at the University of Iowa College of Pharmacy, Division of Medicinal Chemistry and Natural Products, February 19th, 2013, Iowa City, IA.

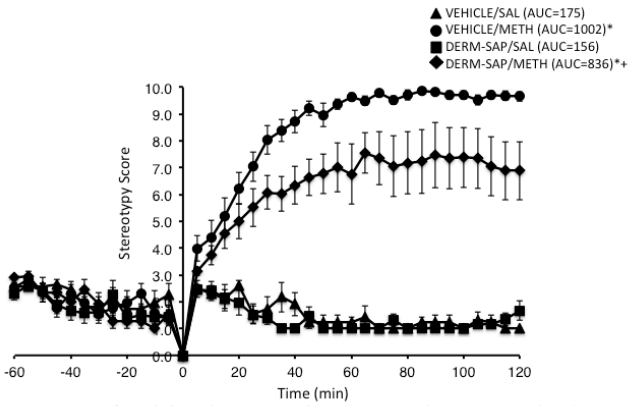


Figure 4. Destruction of patch-based neurons with DERM-SAP reduces METH-induced stereotypy. Values are expressed as the mean ±SEM. Area under the curve (AUC) values are in parentheses. *Significantly different from respective control group, $p<0.005$; +Significantly different from vehicle-pretreated METH-treated group, $p<0.005$. Stereotypy was rated on a scale of 1-10, with 10 representing the highest degree of the response (*Adapted from Murray et al., 2014*).

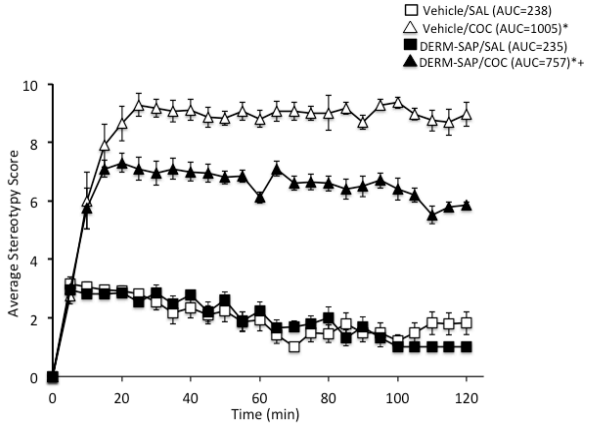


Figure 5. Destruction of patch-based neurons with DERM-SAP reduces cocaine-induced stereotypy. Values are expressed as the mean ±SEM. Area under the curve (AUC) values are in parentheses. *Significantly different from respective control group, $p<0.005$; +Significantly different from vehicle-pretreated cocaine-treated group, $p<0.005$. Stereotypy was rated on a scale of 1-10, with 10 representing the highest degree of the response (*Adapted from Murray et al., 2015*).

IV. Major Accomplishments (INCLUDE UP TO THREE)

A. The role of patch-based neurons in inflexible and repetitive behaviors

One of my major accomplishments was elucidation the role of patch compartment neurons (which are located in the striatum, a component of the basal ganglia) in the development of repetitive behaviors. Stereotypy, which consists of inflexible, repetitive motor activity, is seen in the context of several psychiatric disorders (e.g., Tourette syndrome), but also following psychostimulant exposure. Enhanced activation of the patch compartment is observed with psychostimulant-induced stereotypy, and while many investigators speculated that increased activity in these patch-based circuits underlies repetitive behavior, no studies specifically addressed the role of these neurons in psychostimulant-induced stereotypy. Our laboratory was the first to demonstrate that patch-based neurons contribute to psychostimulant-induced stereotypy by

using a targeted toxin to destroy the neurons of the patch compartment prior to psychostimulant exposure. Our data show that ablation of the patch compartment reduces both methamphetamine- (**Figure 4**) and cocaine-induced (**Figure 5**) and does so by altering the flow of information through the basal ganglia. Data from these studies were presented in poster form at two meetings that were by invitation only: the International Basal Ganglia Society meeting in 2013, and the Gordon Research Conference on the Basal Ganglia in 2016. Enhanced activity of patch-based neurons is also thought to underlie habitual and rewarding behaviors, and we are in the process of investigating this hypothesis. Recent data from our laboratory indicates that patch-based neurons do modulate habit formation, as we have shown that ablation of patch compartment neurons prevents habitual sucrose self-administration and revealing a novel neural pathway for the development of habits (**Figure 6**). These data were presented as a poster at the 2017 Experimental Biology meeting by my Master of Biomedical Sciences student, Terrell Jenrette and comprised Mr. Jenrette's Master's thesis. We are currently preparing a manuscript detailing these findings for submission in December of this year to the journal *Neuroscience*. These studies were supported by an AREA R15 grant from the National Institute on Drug Abuse/NIH, and provided the basis for my new R15 application that is currently pending (see **Pending Grants**, below). We received favorable reviews (see **Pending Grants**), and are in the process of revising this application for resubmission to the NIH in October. There were few major criticisms of this proposal by the reviewers, and we anticipate that our resubmission will be funded.

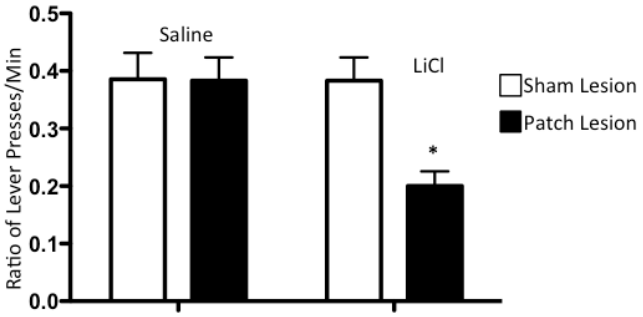


Figure 6. Patch compartment lesions with DERM-SAP reduced habitual sucrose consumption. Animals were first trained to self-administer sucrose, followed by conditioned taste aversion, where the sucrose was paired with an aversive stimulus (LiCl) or saline (as a control). After the taste aversion, animals were re-exposed to sucrose self-administration. Animals that were given saline during the taste aversion continued to self-administer sucrose, as did sham-lesioned animals that were given LiCl. This behavior indicates that the sucrose consumption has become habitual, since habitual behavior is defined as behavior that is insensitive to aversive stimuli (Yin, et al., 2006). However, animals that had patch compartment lesions did not continue to self-administer sucrose after the pairing of sucrose with the aversive stimulus (LiCl), indicating that the behavior is no longer habitual. The data is expressed as the ratio of lever presses per minute for sucrose prior to taste aversion to lever presses per minute for sucrose after taste aversion. *$p<0.05$ vs. SAP-pretreated, LiCl-treated animals; +$p<0.05$ vs. DERM-SAP-treated, saline-treated animals. *Adapted from Jenrette, et al, in preparation.*

This major accomplishment resulted in two publications in reputable peer-reviewed journals, one manuscript in preparation and several poster presentations given at national and international meetings.

Publications:

Striatal patch compartment lesions reduce stereotypy following repeated cocaine administration. Murray RC, Logan MC*, **Horner KA**. *Brain Research* 2015 Aug 27; 1618:286-98. (journal impact factor=2.8)

Striatal patch compartment lesions alter methamphetamine-induced behavior and immediate early gene expression in the striatum, substantia nigra and frontal cortex. Murray RC, Gilbert YE, Logan AS*, Hebbard JC*, **Horner KA**. *Brain Structure and Function* 2014 Jul; 219 (4): 1213-29. (journal impact factor=5.6)

Manuscript in preparation:
Terrell A. Jenrette, Jordan B. Logue and **Kristen Ashley Horner**. Lesions of the patch compartment of striatum reduce habitual behaviors. To be submitted to the journal *Neuroscience,* December 2017. (journal impact factor=3.3)

Poster presentations:
Patch compartment lesions reduce habitual sucrose consumption. **Kristen Ashley Horner**, Jordan B. Logue and Terrell A. Jenrette[#]. To be presented at the Society for Neuroscience Annual meeting, Washington DC, November 11-15, 2017. *#denotes graduate student co-author*

Striatal patch compartment lesions reduce habitual behaviors. Terrell A. Jenrette[#], Jordan B. Logue and **Kristen Ashley Horner**. Presented at the Experimental Biology Meeting, Chicago, IL, April 22-26, 2017. *#denotes graduate student co-author*

Striatal patch compartment lesions attenuate cocaine-induced stereotypy. **Kristen Ashley Horner**, Mary Caroline Logan*, Ryan C. Murray. Presented at the Society for Neuroscience Annual Meeting, Chicago, IL, October 13-17, 2015. *This poster was also presented at a Gordon Research Conference on the Basal Ganglia in March 2016. *denotes undergraduate student co-author*

Kristen Ashley Horner, Ryan C. Murray, Anna S. Logan*, John C. Hebbard *and Yamiece E. Gilbert. Striatal patch compartment lesions alter methamphetamine-induced behavior and immediate early gene expression in the striatum and substantia nigra. Presented at the International Basal Ganglia Society Triennial Meeting, Eilat, Israel, May 3-7, 2013. **denotes undergraduate student co-author*

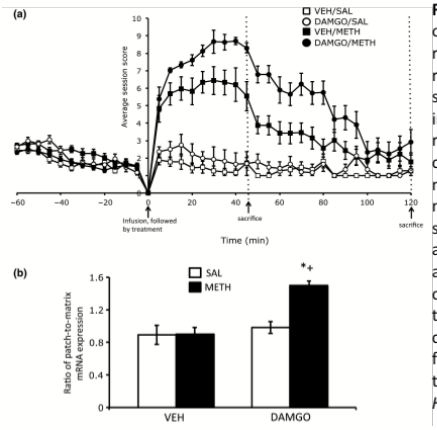


Figure 7. Preferential activation of patch-based mu opioid receptors with the mu opioid receptor-specific agonist, DAMGO significantly increased the intensity of stereotyped repetitive behaviors when combined with a low dose of methamphetamine that induces mild repetitiveness (a). Increased stereotyped behaviors were associated with enhanced relative activation of the patch vs. matrix compartment, as measured by the ratio of patch-to-matrix dynorphin mRNA expression following methamphetamine treatment (b). *Adapted from Horner et al., 2012.*

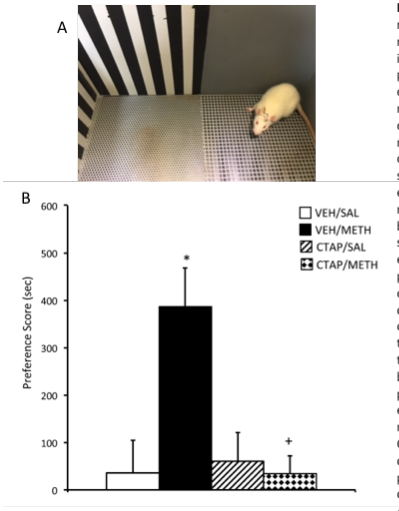


Figure 8. Blockade of patch-based mu opioid receptors reduces methamphetamine-mediated reward, as measured by conditioned place preference (CPP) which is a reliable measure of drug reward. Animals were placed in CPP chambers (A) and underwent drug conditioning for 8 days. This involved giving the animals methamphetamine on even-numbered days, while confined to one side of the chamber and saline on odd-numbered days while confined to the other side chamber. Animals received injections directly into the striatum (where the patch compartment is located) of either vehicle (artificial cerebrospinal fluid) or CTAP (a mu specific antagonist, which will only affect patch-based neurons, as they are the only neurons in the striatum that express mu opioid receptors) prior to each conditioning session. On 9th day, animals were placed in the chamber and allowed access to both sides of the chamber in the absence of drug. The drug is considered rewarding if the animal spends more time on the side of the chamber where drug was given vs the side where saline was given. Our data (B) show that when patch-based mu opioid receptors were blocked with CTAP, animals did not develop a preference for the methamphetamine-paired environment. Values are expressed as the mean (±SEM) number of seconds spent in the drug-paired chamber. Control animals received saline on all 8 days of the conditioning. **p*=significantly different from vehicle-pretreated, saline-treated group; +*p*=significantly different from vehicle-pretreated, METH-treated group. *Adapted from Horner et al, 2017.*

<u>B. The role of patch-based mu opioid receptors in methamphetamine-induced behaviors</u>

A second important discovery was that mu opioid receptors expressed on the neurons of the patch compartment of striatum modulate methamphetamine-induced behaviors. Enhanced activation of patch compartment neurons has been suggested to underlie psychostimulant-induced repetitive behaviors and psychostimulant-mediated reward processes, with modulation by the mu opioid receptors expressed on these neurons. We were the among the first to demonstrate that site-specific manipulation of mu opioid receptors on patch-based neurons altered methamphetamine-induced repetitive

behaviors by altering the balance in activity between the patch and matrix compartments (**Figure 7**). We also demonstrated that site-specific blockade of patch- based mu opioid receptors reduced the rewarding effects of methamphetamine (**Figure 8**), by reducing the enhanced activation of the patch compartment (**Figure 9**). These data point to a novel therapeutic target for the treatment of disorders that are typified by repetitive behaviors (e.g., Tourette syndrome), as well as addiction. The data showing that mu opioid receptor blockade prevented methamphetamine reward was presented as a poster by my undergraduate student, Mary Caroline Logan at the Experimental Biology meeting in April 2016. At this meeting, Ms. Logan was awarded 2nd place in the undergraduate student poster presentation competition, which was sponsored by the American Society for Pharmacology and Experimental Therapeutics. These studies were supported by an AREA R15 grant from the National Institute on Drug Abuse/NIH and provided the foundation for current studies in my laboratory.

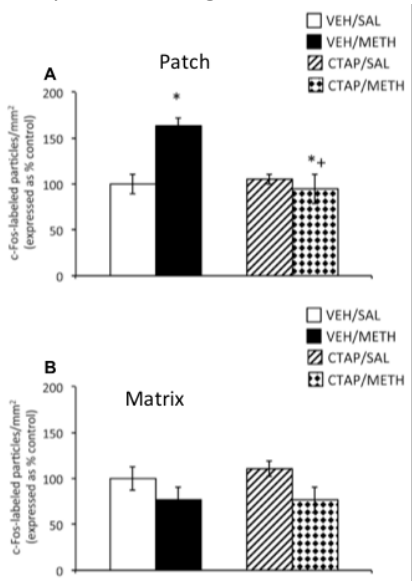


Figure 9. Methamphetamine-induced CPP resulted in enhanced activation of patch neurons (A), as measured by c-Fos levels (a ubiquitous indicator of neuronal activation), an effect that was attenuated by blockade of patch-based mu opioid receptors. There was little effect of methamphetamine or CTAP on the neurons of the matrix compartment (B). *p<0.05 vs. respective saline-treated control group; +p<0.05 vs. vehicle pretreated methamphetamine-treated group. *Adapted from Horner et al., 2017.*

Our discoveries yielded two publications in reputable peer-reviewed journals and an award-winning poster presentation given at a national meeting.

Publications:

Blockade of patch-based μ opioid receptors in the striatum attenuates methamphetamine-induced conditioned place preference and reduces activation of the patch compartment. **Horner KA**, Logan MC*, Fisher TJ*, Logue JB. *European Journal Pharmacology* 2017 Feb 5; 796:207-214. (journal impact factor=2.9)

Activation of mu opioid receptors in the striatum differentially augments methamphetamine-induced gene expression and enhances stereotypic behavior. **Horner KA**, Hebbard JC*, Logan AS*, Vanchipurakel GA*, Gilbert YE. *Journal of Neurochemistry* 2012 Mar; 120(5): 779-94. (journal impact factor=4.1)

Poster presentation:

Blockade of striatal mu opioid receptors attenuates methamphetamine-induced conditioned place preference. Mary Caroline Logan*, Trevor J. Fisher*, Jordan B. Logue and **Kristen Ashley Horner**. Presented at the Experimental Biology Meeting, San Diego, CA, April 2-6, 2016. *This poster won 2nd place in the Best Abstract by an Undergraduate contest sponsored by the American Society for Pharmacology and Experimental Therapeutics.*

**denotes undergraduate student co-author*

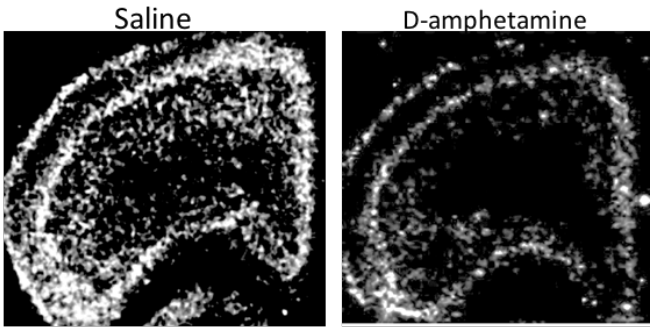


Figure 10. Levels of serotonin 2A (5-HT_{2A}) receptor mRNA were decreased in the prefrontal cortex of animals 24h hours following withdrawal from chronic, escalating doses of D-amphetamine. *Adapted from Murray et al., 2014.*

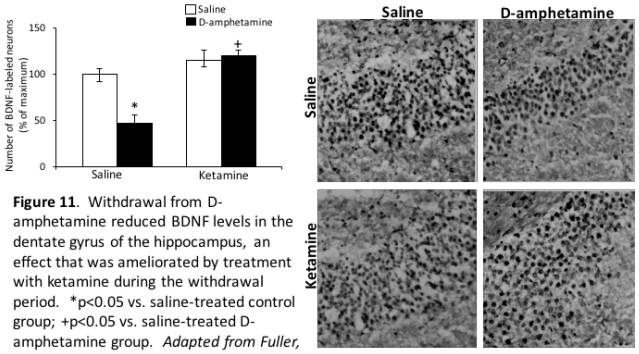


Figure 11. Withdrawal from D-amphetamine reduced BDNF levels in the dentate gyrus of the hippocampus, an effect that was ameliorated by treatment with ketamine during the withdrawal period. *p<0.05 vs. saline-treated control group; +p<0.05 vs. saline-treated D-amphetamine group. *Adapted from Fuller, et al., 2015.*

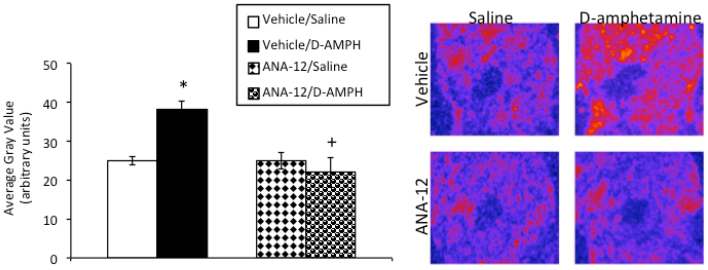


Figure 12. Blockade of BDNF receptors with the Trk-B specific antagonist ANA-12 ameliorated d-amphetamine withdrawal-induced increases dynorphin mRNA expression in the nucleus accumbens. **p<0.05 vs. vehicle-treated saline group; +p<0.05 vs. vehicle-treated D-AMPH group. Adapted from Horner et al., 2014.*

C. Changes in serotonin receptors and brain-derived neurotrophic factor following D-amphetamine withdrawal

A third important discovery by my laboratory was that withdrawal from chronic d-amphetamine treatment down-regulated serotonin receptors in the prefrontal cortex (**Figure 10**) and diminished brain-derived neurotrophic factor (BDNF) levels in the hippocampus. This was a major contribution to scholarship, as changes in BDNF and serotonin receptors following withdrawal from chronic d-amphetamine had not previously been investigated. Serotonin neurotransmission in the prefrontal cortex mediates cognition and BDNF neurotransmission in the hippocampus mediates emotion, and our data indicate that deficiencies in these systems may underlie the withdrawal-induced negative emotional and cognitive states that contribute to relapse. Importantly, we found that treatment with ketamine reversed these deficits (**Figure 11**), revealing a novel therapeutic target that could prevent relapse into drug seeking behaviors and this was an important discovery, as the reversal of d-amphetamine-induced deficits in BDNF had not previously been examined. Interestingly, unlike the hippocampus, BDNF levels are increased in the nucleus accumbens (an area that mediates motivation) following d-amphetamine withdrawal. Our previous work has shown that dynorphin (an endogenous opioid peptide that has dysphoric effects) levels are also increased in the nucleus accumbens during d-amphetamine withdrawal (Horner et al, 2009), and this increase in dynorphin is thought to contribute also to contribute to amphetamine-induced depressive symptoms during withdrawal. Thus, we posited that there may be a relationship between BDNF and dynorphin increases in the nucleus accumbens following d-amphetamine withdrawal, as it has been shown that activation of Trk-B receptors (the preferred receptor for BDNF) can modulate dynorphin expression. We found that blockade of trk-B receptors (which bind BDNF) with ANA-12 during psychostimulant withdrawal prevents up regulation of the opioid peptide dynorphin in the nucleus accumbens (**Figure 12**). Our studies revealed neurochemical changes in the limbic system that may be responsible for the depressive-like symptoms during psychostimulant withdrawal, which could serve as a pharmacological target for the treatment of addiction.

This line of research yielded two publications in reputable peer-reviewed journals and three poster presentations given at national meetings.

Publications:
D-Amphetamine withdrawal-induced decreases in brain-derived neurotrophic factor in sprague-dawley rats are reversed by treatment with ketamine. Fuller JJ[#], Murray RC, **Horner KA**. *Neuropharmacology* 2015 Oct; 97:7-17. (journal impact factor=5.1)

Stress and withdrawal from d-amphetamine alter 5-HT_{2A} receptor mRNA expression in the prefrontal cortex. Murray RC, Hebbard JC*, Logan AS*, Vanchipurakel GA*, Gilbert YE, **Horner KA**. *Neuroscience Letters* 2014 Jan 24; 559:44-9. (journal impact factor=2.2)
**denotes undergraduate student co-author*
[#]denotes graduate student co-author

Poster presentations:
Blockade of TrkB receptors attenuates D-Amphetamine withdrawal-induced increases in dynorphin expression in the nucleus accumbens and striatum. **Kristen Ashley Horner**, Ryan C. Murray and Jasmine J.L. Fuller[#]. Presented at the Society for Neuroscience Annual Meeting, Washington, D.C., November 15-19, 2014. *[#]denotes graduate student co-author*

Investigation into the effects of D-amphetamine on brain-derived neurotrophic factor. Jasmine J.L. Fuller[#], Ryan C. Murray and **Kristen Ashley Horner**. Presented at the Experimental Biology Annual Meeting, San Diego, CA, April 25-30, 2014. *[#]denotes graduate student co-author*

Ryan C. Murray, John C. Hebbard*, Anna S. Logan*, Golda A. Vanchipurakel*, Yamiece E. Gilbert and **Kristen Ashley Horner**. Withdrawal from D-amphetamine alters 5-HT_{2A} receptor expression in the prefrontal cortex and impacts performance on the forced swim test. Presented at the Society for Neuroscience Annual Meeting, New Orleans, LA, October 13-17, 2012.**denotes undergraduate student co-author*

V. Pending Grants
Title: The Role of Patch Compartment Neurons in Reward and Habitual Behavior
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R15 AREA grant
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Andon Placzek, Ph.D., MUSM
Direct Costs: $300,000 for 3 years
In June 2017, this proposal received an overall priority score of 38 (on a scale of 10-100, with a lower score being more favorable). We received very favorable reviews, with only minor weaknesses in our approach, which we can easily address in our revised application (see representative comments and scores below). A revised application will be resubmitted on October 25, 2017. In viewing the scores below, please note that the scale is from 1-10, with 1 being the best score and 10 being the worst score. Based on the comments that we received, we believe that our revised application will be funded.

Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 4
Environment: 1

Overall Impact: The premise of this proposal is that addictive processes are mediated by the patch-matrix system; this hypothesis is based on the observation that drug abuse is persistent and inflexible, and that an imbalance in activity between the patch and matrix systems often underlies inflexible and repetitive behaviors. The hypotheses are clearly stated, and the experimental design is straightforward. Enthusiasm was tempered somewhat by cursory consideration of expected outcomes, alternative outcomes, and rationale for not including female animals. The PI is well suited to conduct the proposed research. Lastly, the proposed research would likely be very interesting to students and would undoubtedly enrich the research environment at Mercer University Macon.

1. Significance:
Strengths

- Drug addiction is a huge public health problem; the proposed studies will improve our understanding of the neural systems that mediate habitual drug abuse.
- The premise is strong and supported by substantial preliminary data.
- The proposed research would undoubtedly enrich the research environment at Mercer University Macon; the plan for student involvement is extensively described.

- The PI has the appropriate expertise to conduct that proposed research and recent related publications.
- The Co-I provides complementary expertise.
- The PI has had previous R15 funding.
- The PI has a strong training history.

3. Innovation:
Strengths

- The patch-matrix system has not been tested as a possible pathway for the development of habitual behaviors.
- More specifically, patch-based circuits have not been examined in drug-related reward processes.

4. Approach:
Strengths

- This is a well-written and clearly understandable grant proposal.
- The extensive preliminary data attest to feasibility and strengthen the premise.
- The pairing of electrophysiology and behavior is a strength.
- The experimental design is appropriate for testing the stated hypotheses, and a power analysis was conducted to determine the number of rats per group.

Weaknesses

- The rationale for using males only is not compelling.
- The expected outcomes and alternative outcomes/counter measures are not sufficiently detailed.
- There is some confusion about whether the studies will include cocaine, methamphetamine, or both; this aspect of the application needs to be clarified.
- There is not discussion of strategies to protect against drug exposure.

5. Environment:
Strengths

- Well qualified students are engaged in research at Mercer.
- There is strong institutional support for research, including the Provost's Mercer University Undergraduate Biomedical Scholar (MUBS) Training Initiative.
- The physical environment appears to be outstanding.

VI. Funded Grants

Federal

Title: The Role of Mu Opioid Receptor Activation in Psychostimulant-Induced Gene Expression in the Patch Compartment of Dorsal Striatum and Repetitive Behaviors
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R15 AREA grant
PI: Kristen Ashley Horner, Ph.D.
Dates: 3/1/09-2/28/14
Direct Costs: $150,000

State/Local

Title: Ketamine treatment for depression following psychostimulant withdrawal
Source: Mercer University Office of the Provost Seed Grant Program
PI: Kristen Ashley Horner, Ph.D.
Dates: 7/1/17-6/30/18
Direct Costs: $4000
This project will be used to generate additional preliminary data that will be used for an upcoming NIH grant application.

Title: Habitual and repetitive behaviors: the role of the patch compartment of striatum
Source: Navicent Community Health Foundation
PI: Kristen Ashley Horner, Ph.D.
Dates: 10/1/2016-9/30/2017
Direct Costs: $14,000
This project will be used to generate additional preliminary data that will be used for an upcoming NIH grant application.

Title: Alterations in basal ganglia circuitry following habit formation
Source: Mercer University Office of the Provost Seed Grant Program
PI: Kristen Ashley Horner, Ph.D.
Dates: 7/1/16-6/30/17
Direct Costs: $3000
This project yielded preliminary data that was used for my most recent NIH grant application (see **Pending Grants***, above)*

Title: The role of the striatal patch compartment in the development of rewarding and habitual behaviors
Source: Mercer University Office of the Provost Seed Grant Program
PI: Kristen Ashley Horner, Ph.D.
Dates: 7/1/15-6/30/16
Direct Costs: $4000
This project yielded preliminary data that was used for my most recent NIH grant application (see **Pending Grants***, above)*

Title: The role of the striatal patch compartment in psychostimulant-induced repetitive and habitual behaviors
Source: Mercer University Office of the Provost Seed Grant Program

PI: Kristen Ashley Horner, Ph.D.
Dates: 7/1/14-6/30/15
Direct Costs: $3000
This project yielded preliminary data that was used for my most recent NIH grant application (see **Pending Grants***, above)*

Title: Methamphetamine-Induced Neurotoxicity and the Disruption of Dopamine Metabolism
Source: Medical Center (MEDCEN) Community Health Foundation/Medical Center of Central Georgia
PI: Kristen Ashley Horner, Ph.D.
Dates: 10/1/2013-9/30/2015
Direct Costs: $20,000
This project yielded preliminary data that was used for two NIH R03 grant applications (both submitted, but not funded; see below)

Title: Brain-derived neurotrophic factor-mediated alterations in dynorphin expression in the limbic system following withdrawal from D-amphetamine
Source: Mercer University Office of the Provost Seed Grant Program
PI: Kristen Ashley Horner, Ph.D.
Dates: 7/1/13-6/30/14
Direct Costs: $3000
This project yielded preliminary data that will be used for an upcoming NIH grant application

VII. Grants submitted, but not funded
Title: Summer Experience in Addiction Research
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R25 Research Education Training grant
Co-PIs: Kristen Ashley Horner, Ph.D., Andon Placzek, Ph.D. (MUSM), Kevin S. Murnane (Mercer University College of Pharmacy)
Direct Costs: $500,000
The NIH Research Education Program (R25) supports research education activities in the mission areas of the NIH. The over-arching goal of this R25 program is to support educational activities that foster a better understanding of biomedical, behavioral and clinical research and its implications. *An initial application was submitted to the National Institute on Drug Abuse in March 2016, and a revised application will be submitted in March 2018.*

Title: Mu Opioid Receptor Modulation of the Patch Compartment of Striatum and Methamphetamine Reward
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R15 AREA Grant
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Andon Placzek, Ph.D., MUSM
Direct Costs: $300,000
Submitted in June 2016 as a revision of the grant below

Title: Mu Opioid Receptor Modulation of the Patch Compartment of Striatum and Methamphetamine Reward
Funding Agency: National Institute on Drug Abuse/NIH

Mechanism: R15 AREA Grant
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Andon Placzek, Ph.D., MUSM
Direct Costs: $300,000
Submitted in February 2016 as a renewal of my R15 grant that ended in 2014 (see **Funded Grants***, above)*

Title: The Role of the Striatal Patch Compartment in Habitual Behavior
Funding Agency: Tourette Syndrome Association
Mechanism: Foundation Research Grant
PI: Kristen Ashley Horner, Ph.D.
Direct Costs: $50,000
Submitted in October 2015 as a preproposal for funding

Title: Methamphetamine neurotoxicity: the role of aldehyde dehydrogenase
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R03 Pilot Grant program
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Jonathan A. Doorn, Ph.D., University of Iowa
Direct Costs: $50,000
Submitted October 2014, as a revision of the grant below; received an impact score of 59

Title: Methamphetamine neurotoxicity: the role of aldehyde dehydrogenase
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R03 Pilot Grant program
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Jonathan A. Doorn, Ph.D., University of Iowa
Direct Costs: $50,000
Submitted in January 2014 as a new application; received an impact score of 45

Title: Methamphetamine-Mediated Disruption of Dopamine Catabolism and Toxicity
Funding Agency: National Institute on Drug Abuse/NIH
Mechanism: R15 AREA grant
PI: Kristen Ashley Horner, Ph.D.
Collaborator/Key Personnel: Jonathan A. Doorn, Ph.D., University of Iowa
Direct Costs: $300,000
Submitted in January 2012 as a new application

DOCUMENTATION OF TEACHING

I. STATEMENT OF PHILOSOPHY OF TEACHING

Today's challenging and ever diverse, yet interdisciplinary, professionalism puts an emphasis in higher education on the development of students' skills in communication, creative and innovative thinking, problem solving, and analytical reasoning in addition to a mastery of multidisciplinary knowledge. To stay informed of these goals in higher education effective teachers should not only devote their efforts to master modern technologies in teaching and pedagogies that have proven to be effective, but more importantly should be acutely aware of students' progress in acquiring skills in metacognition and life-long learning. Recent developments in learning theory and research have suggested that students learn most effectively when they are actively engaged in the learning process. This has led to modern learner-centered pedagogies that have shifted teaching trends from a delivery of information to a mastery of concepts. There are numerous methods that teachers can implement to enhance the active participation of students in class: (1) the teacher serving as an entertainer, (2) adoption of a curriculum based on problem solving, (3) linking of concepts to real situations and promotion of inquiry-guided learning, and (4) peer instruction to enhance student interactions in the learning of core concepts. A good teacher knows how and when to utilize these methods to the maximum benefit of their students. In these active learning processes, whichever approach the instructor chooses to implement in his or her teaching, the role of the instructor should be to serve as a facilitator. The goal should be to promote the students' ability at metacognition rather than to transfer a vast amount of knowledge from a textbook or to be the sole provider of the correct answers to questions. Real life problems, after all, usually do not come with a perfect answer, if there is any answer at all. As educated professionals, once students graduate, their task will typically be to use their skills in problem-solving and analytical reasoning and to devise appropriate solutions in a creative and innovative way. I believe that it is the responsibility of the teacher to prepare students not only to acquire appropriate knowledge but also to possess these necessary skills at problem solving and reasoning.

I believe that a medical educator should be dedicated to life-long learning, facilitate discussion about topics relative to the material at hand, include clinical insights that promote application of the basic sciences, foster conversation about important points in patient care and ask thought-provoking questions. It is my philosophy that I should embody the interdisciplinary thinking and self-directed learning skills that we try to instill in our students. My own study in preparation for teaching responsibilities has provided me with valuable insight into what topics might be difficult for students to comprehend, and how best to assist students with gaining an understanding of the subject matter. However, when I teach, I try not overstate my knowledge, and I attempt to help students develop questions for which they can seek answers from other expert basic scientists, clinicians or other outside resources. I am also eager to give students a helping hand if they encounter a concept that is particularly difficult, but I do so only after the students have given the topic due diligence. According to my evaluations from students, my approach to teaching provides a positive and effective learning environment and students seem to appreciate and praise my efforts in both small and large group sessions. Throughout my years of being a medical educator at MUSM, I've come to realize that clinical medicine is not so different from scientific research, in terms of discovery and the search for answers. Medical students must learn to think in a way that is similar to the way that scientists approach a problem. A patient's condition and a research hypothesis are similar in that both situations present questions that require systematic investigation. As a medical educator, it is my charge to guide students through the problem-solving process by underscoring the subjective and objective aspects of a case, as

well as the assessment of the patient's condition and treatment plan, and by encouraging the students to consider differential diagnoses or alternative treatments, wherever possible.

The overall goal of my teaching is to foster a life-long love of learning, and to equip my students with the tools that they will need to solve the challenging problems that they will inevitably face as a physician. My day-to-day goals as a medical educator are to help medical students build a strong foundation in the principles in pharmacology and to integrate these principles with concepts from other disciplines, for a comprehensive perspective of the basic science that underlies the diagnosis and treatment of clinical conditions. Pharmacology involves understanding the interactions of chemical compounds with living systems, and it is our duty as pharmacologists to help students apply this understanding to the practice of medicine. I also spend a great deal of time familiarizing myself with the topics covered by other disciplines in the courses in which I am involved and point out to my students how these other disciplines relate to the principles and topics covered by pharmacology. For example, when teaching about the drugs used to treat Parkinson's disease, I always emphasize the importance of gaining an understanding of topics related to biochemistry and neuroscience in order to fully comprehend the mechanism of action of certain drugs and their ability to reverse some of the symptoms of this disease. In addition, I make it a point to underscore the importance of putting pharmacology into the context of the organ system being studied. In the monographs that I authored for Brain and Behavior and Block 2, I describe the mechanisms of action of antipsychotic medications in the context of the brain regions involved and how differential regulation of each of these regions provides relief in those suffering from schizophrenia. I believe that these methods of integration help steer students towards a more assimilated and complete view of the material.

Something that I have learned in the decade since I became a faculty member at MUSM, is that effective teaching requires a variety of approaches and detailed organization with a clear presentation of the learning goals. When I first started teaching, I spent a tremendous amount of time organizing and preparing for my lectures and problem-based group sessions. I learned new strategies and skills to make the best use of technology, and studied and tried several well known pedagogies. However, what I've learned from my own teaching experience is that, in addition to these technical aspects of effective teaching, the teacher's enthusiasm for the topics being taught and for the needs of individual students has a tremendous impact on students' learning. While some students have expressed appreciation for the quality and organization of my lectures and group sessions, many more students are appreciative of the feedback that I provide in person or in class and the extra help that I provide outside of the class schedule. I am very enthusiastic about students' learning and believe that it is a teacher's responsibility to assist to the best of his or her ability. I believe that the teacher should foster an effective learning environment that will enable students not only to learn the necessary factual information but also to develop essential skills to facilitate and continue their learning. In turn, I expect that students take responsibility for their education and strive to accomplish their highest level of achievement.

II. EDUCATIONAL CONTRIBUTIONS

A. INSTRUCTIONAL RESPONSIBILITIES

1. Medical Student, Resident and Graduate Teaching

Course/Topic	Activity Format/ Description/Content	Contact Time (Hours per Year)	Years	Number of Learners/ year	Institution/ Comments
Block 2	*See description below*	125	1	Approx. 150	Department of Biomedical Sciences, MUSM
Capstone Course	*See description below*	10	2	6	Department of Biomedical Sciences, MUSM
Neurology Phase	*See description below*	145	9	Approx. 150	Department of Biomedical Sciences, MUSM
Brain and Behavior Phase	*See description below*	60	8	Approx. 150	Department of Biomedical Sciences, MUSM
Hematology Phase	*See description below*	4	7	Approx. 150	Department of Biomedical Sciences, MUSM

Block 2 instructional responsibilities (January 2017-present): Block 2 occurs during the second semester of the first year of medical school, as part of the new medical school curriculum, which was implemented in the fall of 2016. Block 2 is a 16-week block that is divided into four modules, with each module lasting four weeks. The material contained in Block 2 encompasses neurology, behavioral science, the musculoskeletal system and dermatology. I participated in the small-group patient based learning portion of Block 2 for the entire 16-week period, and was responsible for leading small groups of medical students (8 students/group) in the discussion of patient-based clinical cases. I also wrote a monograph for students to use as primary reference for Block 2 (see **Teaching Appendix**) and was responsible for writing test questions in all four modules of Block 2.

As a member of the Block 2 committee, and as an instructor in this block, I was asked by the chair of the Block 2 committee (Dr. Tina Thompson) to oversee the implementation of Module 2 of Block 2, and was responsible for the following: writing the syllabus for Module 2; writing, developing and modifying 14 clinical cases for use in the small-group patient based learning sessions during Module 2 (see **Teaching Appendix**); writing a facilitator guide for faculty that provided background information on the 14 clinical cases I developed for the module (see **Teaching Appendix**); coordinating and recruiting faculty on both campuses for the large-group team-based learning sessions during the module. I also led 5 large-group team based learning sessions (each lasting 2h) during Block 2 covering the following topics: the autonomic nervous system, the eye, degenerative diseases of the central nervous system, the basal ganglia and drugs of abuse. I was solely responsible for developing the educational materials (readiness assessment quizzes, PowerPoint presentations, discussion questions for large group participation) for the degenerative disease, basal ganglia and drugs of abuse large group team-based learning sessions, and contributed material for the autonomic nervous system and eye large group team-based learning sessions. During Block 2, I also served as an instructor in the neuroanatomy lab, which involved

demonstrating neural structures and pathways using brain specimens to small groups of medical students.

Capstone Course instructional responsibilities (2015-present): The capstone course (MED BMS 623 Section M02) is a requirement for all students in the Master's of Science in Preclinical Sciences (MSPCS) program at MUSM. Students must prepare a composition and give an oral presentation on a research topic of their choosing. As a mentor in this course, I meet with individual students that have chosen topics relevant to neuroscience to provide input and guidance regarding their topic. Typically, I mentor 2-3 students each year in this capacity. As an evaluator, I am also responsible for grading compositions and attending and grading oral presentations of the students I've mentored, as well as other students whose topics cover neuroscience (usually 5-6 students total each year).

Neurology Phase instructional responsibilities (2007-2016): For the Neurology phase (which was part of the old BMP curriculum), I served as a small group problem-based learning leader, guiding small groups of medical students (7-8 students/group) in their discussions of patient-based clinical cases. I was also the pharmacology discipline representative for this phase, and in this capacity, I was responsible for writing the pharmacology portion of the study guide and test questions for the final exam. I also served as an examiner for the student oral case analysis exams at the end of the phase. I was also responsible for delivering large-group lectures during this phase. Starting in 2007, and every year thereafter, I delivered a 2h large-group lecture (which was concurrently broadcasted to Savannah, starting in the Spring of 2009) that covered the drug classes relevant to Neurology. In 2015, I assumed responsibility for delivering the large-group lecture on the basal ganglia, which was originally presented by the neuroscience discipline representative (Dr. Tina Thompson) and added an additional large-group lecture covering the autonomic nervous system. I volunteered to deliver the basal ganglia lecture as I have extensive expertise in basal ganglia structure and function. In 2015, I also began teaching neuroanatomy to small groups of students in the wet lab, which previously was taught only by members of the neuroscience discipline. In 2016, I became responsible for lecturing on all motor systems covered in Neurology, which was material that was previously taught by Dr. Thompson.

Brain and Behavior instructional responsibilities (2008-2016): For the Brain and Behavior phase (which was part of the old BMP curriculum), I served as a small group problem-based learning leader, guiding small groups of medical students (7-8 students/group) in their discussions of patient-based clinical cases. I was also the pharmacology discipline representative for this phase, and in this capacity, I was responsible for writing the pharmacology portion of the study guide and writing test questions for the final exam. I also wrote a monograph that served as primary reading for this phase. In addition, I delivered two large-group lectures (which were concurrently broadcast in Savannah) covering pharmacology material for this phase, and served as an examiner for the student oral case analysis exams at the end of the phase.

Hematology Phase instructional responsibilities (2008-2016): For the Hematology phase (which was part of the old curriculum), I served as a pharmacology discipline representative. In this capacity, I was responsible for writing a portion of the syllabus, test questions for the final exam and delivered a 2h large-group lecture (which was concurrently shown in Savannah) on drugs used in this phase.

2. **Describe the experiences you have had with various instructional methods. Examples might include but are not limited to lectures/resource sessions, PBL, TBL, bedside/teaching rounds.**

When I first arrived at MUSM, and began preparing for my upcoming teaching responsibilities in PBL sessions, I was intrigued by the complexity of the case-based method and inherent interdisciplinary nature of this type of curriculum, and was eager to participate in this method of teaching that was so different from the lecture-based teaching in which I'd been trained. In my time teaching in the PBL curriculum, I have found this academic environment both challenging and rewarding. I have enjoyed teaching alongside clinical colleagues and I have been pleased with the interactions that I have with clinicians here at MUSM. I have learned so much from my clinical colleagues, in terms of patient care and how to reach a diagnosis. However, what I've found to be the most rewarding about teaching in the small group PBL sessions is being able to have hands-on participation in the learning process, and to see the growth and development of individual students as they progress through the curriculum. I also found the large group resource sessions that were part of our old curriculum to be an enjoyable experience. It was gratifying to be able to explain concepts that were difficult for students to grasp and to have an opportunity to answer questions that allowed for students to gain a greater understanding of the material. In the fall of 2016, TBL large group sessions were integrated into our curriculum, and these sessions, while challenging and often labor intensive, in terms of preparation, are also very gratifying. These sessions allow me to infuse some lightheartedness and humor into the learning environment, which I believe puts the students at ease and facilitates discussion of difficult topics.

B. CURRICULUM DEVELOPMENT

Item	Course	Dates	Description	Role
Syllabus	Module 2-Block 2	2017	Study guide containing learning objectives for relevant topics and primary reading assignments	Author
Clinical cases	Module 2-Block 2	2017	Clinical cases that were used in small-group patient based learning sessions (14 total)	Author
Facilitator guide	Module 2-Block 2	2017	A guide for faculty containing background information related to the clinical cases	Author
Pharmacology Monograph for Block 2	Block 2	2017	A document containing information on relevant drugs in the Block. This document was also used as a primary reference for the course, meaning that the material in the monograph was testable.	Author
Test questions	Block 2	2017	For use in the weekly formative/summative exams and end of block final exam	Author

Team-based learning materials	Block 2	2017	Materials for use in the TBL sessions included PowerPoint presentations, Quizzes and Discussion questions; these materials were also posted online for the students to use as study tools.	Author
Study guide	Neurology	2007-2016	A guide containing learning objectives for relevant topics and primary reading assignments	Author
Test questions	Neurology	2007-2016	For use in the final exam	Author
PowerPoint presentations	Neurology	2007-2016	Material from large-group lectures that was posted online for students to use as a study tool	Author
Practice questions	Neurology	2014-2016	Short-answer questions designed as a study tool for students, available on the web	Author
Study guide	Brain and Behavior	2008-2016	A guide containing learning objectives for relevant topics and primary reading assignments	Author
Test questions	Brain and Behavior	2008-2016	For use in the final exam	Author
PowerPoint presentations	Brain and Behavior	2008-2016	Material from large-group lectures that was posted online for students to use as a study tool	Author
Pharmacology Monograph	Brain and Behavior	2008-2016	A document containing information on relevant drugs in the Phase. This document was also used as a primary reference for the course, meaning that the material in the monograph was testable.	Author

Practice questions	Brain and Behavior	2014-2016	Short-answer questions designed as a study tool for students, available on the web	Author
Study guide	Hematology	2009-2016	A guide containing learning objectives for relevant topics and primary reading assignments	Author
Test questions	Hematology	2009-2016	For use in the final exam	Author
PowerPoint presentations	Hematology	2009-2016	Material from large-group lectures that was posted online for students to use as a study tool	Author

C. LEARNER ASSESSMENT

Identify the methods in which you have engaged related to assessing learners

Course	**Frequency/Year**	**Learners**	**Role**
Block 2	Every 4 weeks for the entire 16-week block	MS-1	Faculty evaluator of the performance of each student in my small group PBL sessions, with each student receiving a score (with 9 being the maximum) based on the ability of the student to meet specific criteria for small group participation
Neurology	Twice during the 7-week phase	MS-1	Faculty evaluator of the performance of each student in my small group PBL sessions, with each student

			receiving a score between 1-5 (with 5 being the highest) based on the ability of the student to meet specific criteria for small group participation
Neurology	Once, at the end of the phase	MS-1	Faculty evaluator for the end of phase oral examination, which involved giving each student a score from 1-5 (5 being the highest) based on the student's ability to meet our predetermined criteria
Brain and Behavior	Twice during the 5-week phase	MS-2	Faculty evaluator of the performance of each student in my small group PBL sessions, with each student receiving a score of 1-5 (with 5 being the highest) based on the ability of the student to meet specific criteria for small group participation
Brain and Behavior	Once, at the end of the phase	MS-2	Faculty evaluator for the end of phase oral examination, which involved giving each student a score from 1-5 (5 being the highest) based on the student's ability to meet our predetermined

			criteria
Capstone Course	Once, at the end of the course	MSPCS students	Faculty evaluator of written compositions and oral presentations, with each student being assigned a score from 1-5 (5 being the highest) based on the ability of the student to meet the grading rubric

D. ADVISING/MENTORING

1. Graduate Students

Graduate Students Mentored in the Horner Lab, with K.A. Horner as Thesis Committee Chairman

Name	Dates	Degree/ Field of Study	Department/ Institution	Thesis Title
Troy L. Kendrick	1/2017-present	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	The role of the striatal patch compartment in methamphetamine-mediated reward (in progress)
Terrell A. Jenrette*	2016-2017	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	Striatal patch compartment lesions reduce habitual behaviors
Jasmine J.L. Fuller#	2013-2014	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	Investigation into the effects of d-amphetamine on brain-derived neurotrophic factor

**currently enrolled in the M.D. program at MUSM-Macon*
#currently enrolled in the Biomedical Sciences Ph.D. program at Augusta University (formerly Georgia Regents University)

Thesis Committee Service

Name	Dates	Degree/ Field of Study	Department/ Institution	Thesis Title

Catherine Cater Starling (Committee chair: A.N. Placzek)	2016-2017	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	Using patch clamp electrophysiology to detect changes in excitatory synaptic strength in the striatum of rats treated with methamphetamine
Jordan B. Logue (Committee chair: A.N. Placzek)	2014-2015	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	Mouse strain differences in Ca^{2+}-activated potassium (SK) channel function in midbrain dopamine neurons regulate differential firing in adolescence
Chelsey D. Faircloth (Committee chair: A.N. Placzek)	2013-2014	M.S. in Biomedical Sciences	Department of Biomedical Sciences, MUSM	Age-dependent differences in SK channel function modulate the excitability of VTA DA neurons

2. Medical Students

Medical Student Academic Advising

Name	Dates	Degree	Department/ Institution	Comments
Taylor Hollingsworth	2017-present	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Melanie Wanigatunga	2016-present	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Gregory Morgan	2016-present	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Megan Sando	2016-present	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Lauren Lewis	2015-present	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Cameron Wes Lovell	2015-2017	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Mary Hannah Read	2015-2017	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Anna Tadsen	2014-2016	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Frances Cobb	2014-2016	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Joshua Masdon	2014-2016	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Rachel Saporito	2013-2015	M.D.	Department of Biomedical	Preclinical academic advisor

			Sciences, MUSM	
Joseph Kinuthia	2013-2015	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor
Jacob Kirkpatrick	2013-2015	M.D.	Department of Biomedical Sciences, MUSM	Preclinical academic advisor

3. Postdoctoral fellow, research associates, residents:

Name	Dates	Degree/ Field of Study	Department/ Institution	Comments
Katayoun Sedaghat, Ph.D.	2011	Post-doctoral fellow	Department of Biomedical Sciences, MUSM	Project title: The role of the striatal dynorphin system in methamphetamine-induced behaviors

E. Educational Leadership and Administration

I was in charge of the development of the curricular material for Module 2 of Block 2.

III. PROFESSIONAL DEVELOPMENT

Course/ Activity/Description	Dates	Location	# of hours
American Society for Biochemistry and Molecular Biology webinar, "The Future of the Biomedical Research Workforce"	June 2017	MUSM-Macon	1h
National board of medical examiners question writing workshop	July 2016	MUSM-Macon	4h
MUSM Angoff method of assessment workshop	May 2016	MUSM-Savannah	8h
MUSM Team-based learning workshop	October 2015	MUSM-Macon	4.5h
American Association of Medical Colleges Grant writing workshop	September 2015	Atlanta, GA	8h
American Society for Pharmacology and Experimental Therapeutics Teaching Institute: Practical Technologies for Effective Teaching	April 2014	San Diego, CA	2.5h

IV. EVALUATION OF TEACHING

Summary of teaching evaluations since appointment to Associate Professor in September 2012

1. Neurology Phase, 2013-2016

A. Neurology, Spring 2013

i. Evaluation of faculty performance in small group PBL sessions by 1st year medical students

Number of learners: 6
100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

Dr. Horner is such a good tutor. She facilitates discussion very well. She is one of the best tutors I've had so far.

Dr. Horner was very encouraging throughout the phase. I was very pleased with how easy it was to get into touch with her. She was always looking to help us find answers to our questions if she did not know it off the top of their head.

Dr. Horner was very knowledgeable on the information that was presented to us. It was especially helpful in the neuroscience portion as well as the pharmacology. If she did not know something she would help us figure it out through her own sources.

I was very pleased with the way Dr. Horner treated us. She was respectful of us and how important our education was. She is dedicated to our success and it made me want to work hard.

ii. Evaluation of faculty as SOCA (oral exam) examiner by 1st year medical students

Number of learners: 8

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	4	4	**8**	**2.5**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	4	4	**8**	**2.5**
c. did not interrupt your presentation with "fact-finding questions.	0	4	4	**8**	**2.5**
d. did not ask inappropriate questions at the end of your presentation.	0	4	4	**8**	**2.5**
e. did not keep you beyond the 45-minute limit.	0	4	4	**8**	**2.5**
f. informed you with useful feedback in a timely manner.	0	4	4	**8**	**2.5**
g. provided you with constructive criticism.	0	4	4	**8**	**2.5**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	4	4	**8**	**2.5**
6. Did you agree with your examiners' feedback of your performance?	0	4	4	**8**	**2.5**
	0	36	36	**72**	**2.5**

Comments from students:

I felt confident going into my soca and Dr. Horner gave me great constructive feedback following my presentation.

B. Neurology, Spring 2014

i. Evaluation of faculty performance in small group PBL sessions by 1st year medical students

Number of learners: 6

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

Dr. Horner is a great tutor!! She explains concepts so well and really makes sure we stay on task. She doesn't let us get bogged down in the details which is so easy to do in Neuro.

Dr. Horner has a very positive attitude. She was very accessible, and always encouraging. She helped keep our group calm and focused.

Dr. Horner really knew her stuff. With her pharmacology and neuro background she definitely was the perfect tutor to have for the most challenging concepts.

I really can't think of anything she could do better, I feel very lucky to have had her as a tutor for this phase. Her knowledge base was impressive and she is also a great person. I really enjoyed our group, and I feel like I got a lot out of our time together.

ii. Evaluation of faculty as SOCA (oral exam) examiner by 1st year medical students

Number of learners: 8

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	4	4	**8**	**2.5**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	4	4	**8**	**2.5**
c. did not interrupt your presentation with "fact-finding questions.	0	4	4	**8**	**2.5**
d. did not ask inappropriate questions at the end of your presentation.	0	4	4	**8**	**2.5**
e. did not keep you beyond the 45-minute limit.	0	4	4	**8**	**2.5**
f. informed you with useful feedback in a timely manner.	0	4	4	**8**	**2.5**
g. provided you with constructive criticism.	0	4	4	**8**	**2.5**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	4	4	**8**	**2.5**
6. Did you agree with your examiners' feedback of your performance?	0	4	4	**8**	**2.5**
	0	36	36	**72**	**2.5**

Comments from students:

Dr. Horner asked appropriate questions and was very pleasant.

I greatly appreciated Dr. Horner's encouragement during my presentation. She seemed very engaged while listening, and provided valuable feedback afterwards. Thank you for your guidance.

C. Neurology, Spring 2015

i. Evaluation of faculty performance in small group PBL sessions by 1st year medical students

Numbers of learners: 7

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

Dr. Horner was very knowledgeable and helpful in the neurology phase. She was accessible for questions, enthusiastic about the subject matter, and encouraged the PBL process. She made neurology a pleasant phase. I would love to have her again in the future!

Dr. Horner was always positive and interested in the group process. She encouraged us, but was also accessible for questions and idealistic about the goals for the group.

Dr. Horner was extremely knowledgeable on the phase content and helped us make clinical connections with the basic sciences. She was always on time and prepared for group, with a positive attitude.

Dr. Horner was always respectful, understanding, and professional when addressing curricular and extracurricular issues.

ii. Evaluation of faculty as SOCA (oral exam) examiner by 1st year medical students

Number of learners: 8

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	1	7	**8**	**2.9**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	1	7	**8**	**2.9**
c. did not interrupt your presentation with "fact-finding questions.	0	1	7	**8**	**2.9**
d. did not ask inappropriate questions at the end of your presentation.	0	1	7	**8**	**2.9**
e. did not keep you beyond the 45-minute limit.	0	1	7	**8**	**2.9**
f. informed you with useful feedback in a timely manner.	0	1	7	**8**	**2.9**
g. provided you with constructive criticism.	0	1	7	**8**	**2.9**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	2	6	**8**	**2.8**
6. Did you agree with your examiners' feedback of your performance?	0	1	7	**8**	**2.9**
	0	10	62	**72**	**2.9**

Comments from students:

Dr. Horner was very well prepared and respectful throughout the oral presentation.

She seemed prepared and offered useful feedback regarding pharmacology.

D. Neurology, Spring 2016

i. Evaluation of faculty performance in small group PBL sessions by 1st year medical students

Number of learners: 7

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

It was incredibly helpful to have a pharmacologist as a tutor for neuro, especially with the intro to ANS pharm. Dr. Horner was great at keeping our group on task and keeping us focused on the right material. Any time we asked for additional resources she provided them for us. I would love to have her as a tutor again.

Dr. Horner always had a good attitude, she treated each student with respect and was interested in the material we discussed. She was very positive in all our group sessions.

She was extremely knowledgeable and very well prepared, if she wasn't able to answer a question, she would go look it up and come back to the next group with the answer. I really loved having Dr. Horner as a tutor, she was kind and helpful and I would definitely want to have her as a tutor again!

She was very professional, positive, and helpful in group. I really liked the fact that she would give us constructive criticism and tell us if we were way off base when discussing the subject matter. She always made sure we stayed on track.

ii. Evaluation of faculty as SOCA (oral exam) examiner by 1st year medical students

Number of learners: 8

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	0	8	**8**	**3.0**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	0	8	**8**	**3.0**
c. did not interrupt your presentation with "fact-finding questions.	0	0	8	**8**	**3.0**
d. did not ask inappropriate questions at the end of your presentation.	0	0	8	**8**	**3.0**
e. did not keep you beyond the 45-minute limit.	0	0	8	**8**	**3.0**
f. informed you with useful feedback in a timely manner.	0	0	8	**8**	**3.0**
g. provided you with constructive criticism.	0	0	8	**8**	**3.0**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	0	8	**8**	**3.0**
6. Did you agree with your examiners' feedback of your performance?	0	0	8	**8**	**3.0**
	0	0	72	**72**	**3.0**

Comments from students:

Dr. Horner was a very professional and helpful SOCA grader.

Great case and great evaluator!

2. Brain and Behavior Phase, 2013-2015

A. Brain and Behavior, Fall 2013

i. Evaluation of faculty performance in small group PBL sessions by 2nd year medical students

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

I would definitely have Dr. Horner as a tutor again. Dr. Horner does a good job of guiding the group through the material as well as making sure that we touch on the topics in appropriate detail. I thought that she was very helpful in group would allow students to attempt to explain a topic then clearing up any points not discuss or needing clarification.

Dr. Horner's attitude toward our group was that of a good tutor. She was enthusiastic and respectful to each member of the group and allowed each person the chance to speak and she offered advice in a clear and respectful manner.

Dr. Horner's medical knowledge was comprehensive to me. She was not just knowledgeable about her particular discipline. It was obvious that she spent time learning the material in the other disciplines and knew that material in addition to pharmacology, which was much appreciated by the group. She was also not afraid to use real life stories as examples of the psychological and social impacts on medicine.

Dr. Horner helped us stay on track and focused, she is committed to helping us make the most out of BMP time. She allowed group discussion appropriately, and interjected when we were confused or did not fully discuss a topic. She helped us stay on track with completing each of the cases associated with the phase. I would definitely chose to have Dr. Horner again as a tutor, it was a very productive group.

ii. Evaluation of faculty as SOCA (oral exam) examiner by 1st year medical students

Number of learners: 7

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	1	6	**7**	**2.9**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	1	6	**7**	**2.9**
c. did not interrupt your presentation with "fact-finding questions.	0	1	6	**7**	**2.9**
d. did not ask inappropriate questions at the end of your presentation.	0	1	6	**7**	**2.9**
e. did not keep you beyond the 45-minute limit.	0	2	5	**7**	**2.7**
f. informed you with useful feedback in a timely manner.	0	2	5	**7**	**2.7**
g. provided you with constructive criticism.	0	2	5	**7**	**2.7**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	2	4	**6**	**2.7**
6. Did you agree with your examiners' feedback of your performance?	0	2	5	**7**	**2.7**
	0	14	48	**62**	**2.8**

Comments from students:

Dr. Horner is the best SOCA grader I've had so far. She made sure to put me at ease, and was helpful in drug pronunciations.

This case was well written, and Dr. Horner did an excellent job as my SOCA examiner.

B. Brain and Behavior, Fall 2014

i. Evaluation of faculty performance in small group PBL sessions by 2nd year medical students

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

Dr. Horner is a fantastic tutor. She is able to fill in gaps that we struggle with, she stimulates good discussions and she is really nice.

Dr. Horner was always humble, respectful, accessible, and interested in what we had to say during group.

Dr. Horner was especially knowledgeable about pharm and neuro. For all other subjects, she read the assigned reading so that she was clued in.

Dr. Horner was always professional yet friendly at the same time. She did a great job in helping us push through the material when it seemed that we were becoming "burned out."

ii. Evaluation of faculty as SOCA (oral exam) examiner by 2nd year medical students

Number of learners: 8

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	2	6	**8**	**2.8**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	2	6	**8**	**2.8**
c. did not interrupt your presentation with "fact-finding questions.	0	2	6	**8**	**2.8**
d. did not ask inappropriate questions at the end of your presentation.	0	2	6	**8**	**2.8**
e. did not keep you beyond the 45-minute limit.	0	2	6	**8**	**2.8**
f. informed you with useful feedback in a timely manner.	0	2	6	**8**	**2.8**
g. provided you with constructive criticism.	0	1	6	**7**	**2.9**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	1	1	6	**8**	**2.6**
6. Did you agree with your examiners' feedback of your performance?	0	2	6	**8**	**2.8**
	1	16	54	**71**	**2.7**

Comments from students:

I felt that Dr. Horner was very fair with the questions she asked. Her facial expression and mannerisms during my presentation were positive, which helped ease my nerves.

Overall, Dr. Horner was a great SOCA evaluator and asked relevant questions to the case.

C. Brain and Behavior, Fall 2015

i. Evaluation of faculty performance in small group PBL sessions by 2nd year medical students

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:

Dr. Horner did a great job leading us and helping us understand what we needed to know with each discipline.
Dr. Horner always had a positive attitude in group and was always very helpful.
Dr. Horner's expertise was especially strong in this phase. She is also knowledgeable about disciplines outside her own field of research.

Dr. Horner brought expertise in both neuroscience and pharmacology to the table. I was very grateful to have her insight in two different and difficult subject areas.

Evaluation of faculty as SOCA (oral exam) examiner by 2nd year medical students

Number of learners: 8 (two students did not complete the evaluation)

Assessment of oral evaluator:

	disagree	agree	strongly agree	N	Mean
a. seemed appropriately prepared	0	2	4	**6**	**2.7**
b. allowed you the time you required (up to 20 minutes) for your analysis presentation.	0	2	4	**6**	**2.7**
c. did not interrupt your presentation with "fact-finding questions.	0	2	4	**6**	**2.7**
d. did not ask inappropriate questions at the end of your presentation.	0	2	4	**6**	**2.7**
e. did not keep you beyond the 45-minute limit.	0	2	4	**6**	**2.7**
f. informed you with useful feedback in a timely manner.	0	2	4	**6**	**2.7**
g. provided you with constructive criticism.	0	2	4	**6**	**2.7**
h. seemed to evaluate integrative, analytical skills more than cognitive skills.	0	2	4	**6**	**2.7**
6. Did you agree with your examiners' feedback of your performance?	0	2	4	**6**	**2.7**
	0	18	36	**54**	**2.7**

Comments from students:
Dr. Horner was great to have for the evaluator.

3. Block 2: Neurology, Behavioral Science, Musculoskeletal System and Dermatology

A. Evaluation of faculty performance in small group PBL sessions by 1st year medical students

i. Module 1, January-February, 2017

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:
Dr. Horner was both knowledgeable and an effective teacher; she guided discussion to help each student contribute. I like that she was straightforward and always willing to talk about whatever topics we wanted to talk about.

Dr. Horner was positive and interested in what the students had to say. She listened to our suggestions and we were able to adapt our group to be more productive. She was ready to work right when walking in the room and did not want to waste time. This made for productive meetings.

This area was Dr. Horner's best attribute. She was very specialized in this field, and it enabled us, as students, to gain a good understanding of not just the basics of the material, but the underlying reasons for the concepts.

Dr. Horner displayed a great amount of professionalism. She expected the students to come prepared, and appropriately kept us on task. She was fantastic. I would love to have her again.

ii. Module 2, February-March, 2017

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:
Dr. Horner is very knowledgeable about the depth of information that we need to know. I have had other tutors who allow groups to fall down rabbit holes to nowhere and are complicit in allowing us to do so. Dr. Horner keeps the group on task and focuses students to what is actually relevant.

Dr. Horner was always very pleasant, respectful, and accessible if we had questions.

This was my first experience with a tutor who was an expert in the field that we were currently studying for the whole module. It made a huge impact and my scores reflect that.

It was obvious Dr. Horner is very knowledgeable in her field and that she prepared for concepts outside of her expertise.

iii. Module 3, March-April, 2017

Number of Learners: 8

100% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:
Dr. Horner was a delight to have as our tutor for this module - she provided sound advice while being very respectful to all of the students.

Dr. Horner always presented a positive and encouraging attitude. Excellent knowledge of pharmacology.

We were lucky to have her pharmacological expertise this previous module.

Provided a great environment for learning and was a good example for the students as to what professionalism is

iv. Module 4, April-May, 2017

Number of Learners: 8

88% students surveyed said they would choose to have Dr. Horner again as a tutor

Comments from students:
Dr. Horner has such a breadth and depth of knowledge. She tends to be straight-to-the-point and ready to work.

Dr. Horner seemed interested, respectful, and offered help outside of small group.

Dr. Horner has an encyclopedic knowledge of neuroanatomy and associated pharmacology.

I could tell that Dr. Horner wanted to be efficient with the group's time because she encouraged us to plan how we would spend each session. She was able to encourage us to pursue thoughtful discussions while gently nudging us away from "rabbit holes." I appreciated her openness to all group members and suggestions for topics to cover.

V. TEACHING APPENDIX

Pharmacology Monograph for Module 2
Spring 2017

Memantine for the treatment of Alzheimer's Disease (Module 2)

Rohypnol, Dextromethorphin, Buprenorphine (Module 2)

Drugs for the treatment of ADHD (Module 3)

Atypical antipsychotics: interactions between
the dopamine and serotonin systems (Module 3)

Hypnotics (Module 3)

Drugs for Migraine (Module 4)

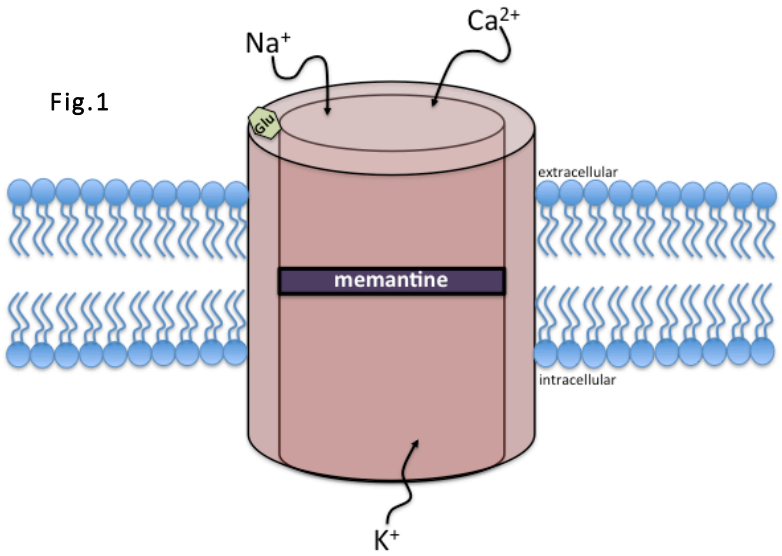
Dr. Horner

Memantine for the treatment of Alzheimer's Disease (Module 2)

Pharmacodynamics

Memantine is approved for the treatment of moderate to severe Alzheimer's disease. Recent studies indicate that memantine may also improve cognitive symptoms in patients with mild to moderate Alzheimer's disease and may also effective against vascular dementia. Memantine is a non-competitive NMDA glutamate receptor antagonist that acts by directly blocking the ion channel of the NMDA receptor complex by binding to the Mg^+ site within the channel (**Fig. 1**). It does not compete directly with glutamate at the binding site for the excitatory neurotransmitter. Instead, memantine blocks the channel in a voltage-dependent fashion, which means that the channel must be open in order for the drug to enter the channel and the Mg^+ that is normally bound to the channel at resting membrane potential has dissociated (recall that Mg^+ dissociates from the channel when the membrane is depolarized). Memantine also binds to the receptor with moderate affinity, so it has a relatively fast on- and off-rate at its binding site within the channel. Other NMDA receptor antagonists known to directly block the channel, but which are not used for the treatment of dementia, are ketamine and phencyclidine (PCP).

Fig.1



Memantine blocks the ion channel of the NMDA receptor, but does not compete with glutamate (Glu) for its binding site on the receptor.

NMDA receptors are present in high concentrations in the cortex and hippocampus. NMDA receptors are ligand *and* voltage gated channels through which Na^+, Ca^{2+}, and K^+ pass. Normally, these receptors are involved in the long-term potentiation that contributes to learning and memory formation. However, several lines of evidence suggest that sustained low-level elevations of glutamatergic activity may actually contribute to the pathology of Alzheimer's disease. Aß peptide has been shown to increase glutamate release upon neuronal depolarization, and can bind directly to a site on the NMDA receptor. Aß peptide has also been shown to decrease uptake of glutamate by glial cells. Astrocytes from patients with Alzheimer's disease are less efficient at taking up glutamate. Overall, it is thought that these events may lead to excess levels of extracellular glutamate, and it is this excess glutamate that may contribute to the pathology of Alzheimer's disease. This hypothesis is based on the observation

that excess glutamate can cause excitotoxic neuronal injury, probably by increasing intraneuronal concentrations of Ca^{2+}.

Memantine is thought to be effective in treating Alzheimer's, without producing the adverse psychotic side effects associated with other channel blockers like PCP, largely due to the kinetics of its binding. It is thought that memantine effectively blocks the postsynaptic excitatory activity of the *moderately* high levels of glutamate (in the μM range) that are postulated to be tonically present in Alzheimer's (as described above), but to allow the activity caused by the *very high* levels of glutamate (in the mM range) that occur upon firing of glutamatergic neurons. Because of its lower affinity (and therefore, higher rate of dissociation from its intra-channel binding site), memantine is more likely to leave the channels when many of the channels are open. This is different from NMDA antagonists like PCP, which do not leave the channel readily, even when it is open, because they have a higher affinity and therefore a slower off-rate from their binding site.

Another property of memantine, which is not given much attention, is that is acts as an antagonist at $5HT_3$ receptors with about the same affinity with which it binds to the NMDA receptor. $5HT_3$ receptors are ionotropic receptors that cause excitatory neuronal activity. $5HT_3$ antagonism has been shown to enhance learning and memory.

Pharmacokinetics

Memantine is given orally and is completely absorbed from the GI tract. The drug is not metabolized by the P450 system, and no interactions have been reported with drugs that are metabolized by this system. Although some inactive metabolites have been identified, most of the drug is excreted unchanged by the kidney, undergoing both renal tubular secretion and re-absorption by cationic transport proteins. Excretion is pH dependent, and is reduced if the urine becomes more alkaline (therefore, avoid drugs that alkalinize the urine, such as carbonic anhydrase inhibitors and/or sodium bicarbonate). Co-administration with donepezil does not affect its metabolism.

Clinical Pharmacology

Memantine has been shown to significantly decrease the rate of progression of symptoms of Alzheimer's disease. Significantly less decline in activities of daily living, performance-based cognitive function, and the clinician's interview-based impression of change were seen in memantine-treated groups compared to placebo controls after 28 weeks, although both groups showed decline from their pretreatment baselines. A decrease in caregiver time and requirement for institutionalization was also seen with memantine.

When combined with donepezil, a cholinesterase inhibitor, memantine caused an even greater improvement in cognitive function. Patients treated with the combination of drugs showed an improvement in cognitive function over their starting baseline, while those treated with donepezil alone showed a gradual decline. Patients treated with the combination of drugs showed

deterioration in their ability to perform the activities of daily living, but the decrease was less than in those treated with donepezil alone.

Drug interactions

Amantadine, dextromethorphan, and ketamine are all known to act as antagonists at the NMDA receptor and should not be co-administered to patients receiving memantine.

Rohypnol and Dextromethorphan (Module 2)

Rohypnol

Rohypnol (flunitrazepam; often called "roofies") is a benzodiazepine, as it binds specifically to $GABA_A$ receptors, which underlies its sedative effects. Rohypnol is not approved for medical use in the United States, and its importation is banned. Aside from its use as a psychoactive agent by those attending raves, Rohypnol has also been used as a "date rape drug". Rohypnol is colorless, odorless and tasteless, making it easy to add it beverages, where it is ingested unbeknownst to the victim. When rohypnol is combined with ethanol, the victim becomes incapacitated and unable to resist sexual assault. Rohypnol can produce anterograde amnesia, in which individuals may not remember events they experienced under the influence of the drug. Like other benzodiazepines, repeated use of Rohypnol can lead to tolerance and dependence. Rohypnol may be lethal when combined with ethanol or other CNS depressants. Treatment for Rohypnol dependence is similar to the protocol used for any benzodiazepine, which may consist of a brief detoxification period, with 24-hour intensive monitoring, since withdrawal from benzodiazepines can be life-threatening.

Dextromethorphan

Dextromethorphan is a widely available cough suppressant, commonly found in OTC medications, such as Robitussin (which why dextromethorphan is often called "Robo"), that when taken in high doses, produces dissociative effects similar to what is seen with ketamine or PCP. Remember that dissociative drugs distort perception of sight and sound, and produce feelings of detachment and dissociation-from both self and the environment, but despite these mind-altering effects, do not generally produce hallucinations, although hallucinations with dextromethorphan have been reported. Like ketamine and PCP, dextromethorphan blocks N-methyl-D-aspartate (NMDA)-type glutamate receptors. Glutamate is involved in the perception of pain, responses to the environment and memory. While glutamate is considered the major excitatory neurotransmitter in the brain, it is also a major modulator of inhibitory tone. For example, NMDA receptors are found on neurons that contain GABA; these GABAergic neurons constitute inhibitory pathways that decrease the activity of major excitatory pathways. When there is a blockade of NMDA receptors on these inhibitory pathways, the inhibitory pathways are no longer able to function, leading to a disinhibition of major excitatory pathways, which is thought to underlie the distorted perception that is seen with these types of drugs. Dextromethorphan should not be combined with MAO inhibitors, or within 2 weeks of using a MAO inhibitor; combining the two may result in motor restlessness, tremor, extreme

hyperpyrexia and potentially death. These effects are thought to be due to potentiation of 5-HT neurotransmission, as dextromethorphan also has the ability to block the reuptake of 5-HT from nerve terminals.

Buprenorphine (Module 2)

Buprenorphine is FDA-approved for the treatment of opioid addiction. Buprenorphine is an opioid compound that binds to mu opioid receptors. However, the unique pharmacological characteristics of buprenorphine provide a decreased risk of respiratory depression or overdose, as compared to other opioids, such as methadone, heroin or morphine.

Buprenorphine is a partial agonist at mu opioid receptors. The rewarding, analgesic and respiratory depressant effects of opioids are the result of mu opioid receptor activation. Unlike the mu opioid receptor agonists that are typically abused, most of which are full agonists at the mu opioid receptor, buprenorphine is a partial agonist at the mu opioid receptor. What this means is that buprenorphine only partially stimulates mu opioid receptors. Buprenorphine will still yield the same effects (e.g., euphoria, analgesia) as full mu opioid receptor agonists (e.g., heroin, methadone), but with less intensity. Buprenorphine is moderately psychoactive, which is thought to reduce craving in patients, and increase compliance with the treatment regimen. It is also important to note that because buprenorphine is a partial mu opioid receptor agonist, it will act as an antagonist in the presence of a full mu opioid receptor agonist. If a patient that is taking buprenorphine then takes another mu opioid receptor agonist, such as heroin, buprenorphine will prevent heroin from interacting with mu opioid receptors, thereby blocking the effects of heroin.

Buprenorphine binds with high affinity to mu opioid receptors. Although buprenorphine only partially activates mu opioid receptors, it binds to the mu opioid receptor with high affinity. Buprenorphine has a higher affinity for the mu opioid receptor than other commonly abused mu opioid receptor agonists. Remember that the affinity of a drug is a measure of how strongly that drug binds to the receptor. It is important to note that if a patient has already taken another mu opioid receptor agonist, and is then given buprenorphine, the buprenorphine will displace the other opioid from the mu opioid receptor, owing to buprenorphine's higher relative affinity for the mu opioid receptor. Because of this effect, the physician must take care in initiating buprenorphine therapy for the opioid dependent patient. The abrupt displacement of the abused opioid from the mu opioid receptor by buprenorphine can precipitate acute withdrawal. Factors such as the dose of buprenorphine, the individual's level of physical dependence, and the amount of time since the last administration of the abused opioid must be taken into consideration when initiating buprenorphine treatment.

Buprenorphine dissociates slowly from mu opioid receptors. In other words, buprenorphine will detach very slowly from mu opioid receptors, which most likely why buprenorphine has a long duration of action.

Buprenorphine acts as an antagonist at kappa opioid receptors. Activation of kappa opioid receptors results in dysphoria, and stimulation of these receptors during opioid withdrawal may

underlie the depression that is commonly seen in those experiencing opioid withdrawal. Importantly, withdrawal-induced depression may contribute to the relapse into drug-taking behaviors, as an attempt by the opioid-dependent individual to alleviate their dysphoria. Blockade of kappa opioid receptors by buprenorphine may help alleviate withdrawal-induced depression, and could reduce the likelihood of relapse.

Buprenorphine is available in two formulations, both of which are administered sublingually: **subutex** (buprenorphine HCl) and **suboxone** (buprenorphine HCl + naloxone HCl, which is an opioid receptor antagonist). Both compounds produce similar effects when taken sublingually. However, suboxone was developed because subutex has the potential for abuse. Naloxone, unlike buprenorphine, is poorly absorbed when administered sublingually. But if suboxone is injected by a person that is opioid-dependent, the naloxone (which is readily absorbed by the iv route), will precipitate acute withdrawal. This is thought to serve as a deterrent to the abuse of suboxone by injection.

Drugs used for the treatment of ADHD (Module 3)

The dose makes the poison

Stimulants, such as methylphenidate and amphetamine are the most common drugs for the treatment of ADHD. For many years it was thought that stimulants had paradoxical calming effects in those that suffered from ADHD, but stimulating effects in normal individuals. This misconception stemmed from the fact that when humans abuse these compounds, the doses are relatively high, resulting in significant increases in motor activity, i.e., hyperactivity. However, we now know that stimulants, when given in *low doses* (such as the doses that are given therapeutically) can actually focus attention, improve executive function and reduce motor activity, in both normal and ADHD subjects.

Neurobiological basis of therapeutic effects

The ability of stimulants to decrease hyperactivity and increase attentional focus in both normal and ADHD subjects is thought to be due to modulation of dopamine (DA) and norepinephrine (NE) neurotransmission in the *prefrontal cortex*. The prefrontal cortex is an important region for regulation of attention and motor activity, and this region receives dense inputs from brainstem nuclei. Specifically, DA inputs to the prefrontal cortex arise from the ventral tegmental area, while NE inputs arise from the locus coeruleus (**Fig. 2**). Moderate levels of DA and NE in the prefrontal cortex are needed for optimal cognitive and behavioral function. It is thought that those that suffer from ADHD most likely have deficient DA/NE transmission in the prefrontal cortex, resulting in poor attention, diminished executive function and increased hyperactivity. Therefore, compounds that increase DA/NE levels to the "normal" range in the prefrontal cortex result in improved attention and decreased hyperactivity. The stimulants used to treat ADHD act on the DA and NE transporters located presynaptically on dopaminergic and noradrenergic terminals in the prefrontal cortex. These compounds increase DA/NE neurotransmission either by blocking the reuptake of DA and NE by their respective transporters (e.g., methylphenidate)

or by reversing the DA and NE transporters, resulting in increased DA and NE release into the synapse (e.g., amphetamine).

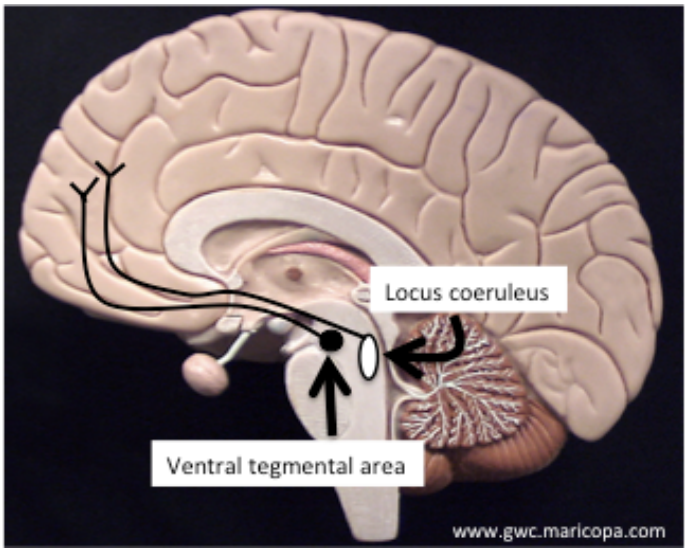


Fig. 2. Brainstem projections to the frontal cortex. The neurons in the ventral tegmental area contain dopamine, while those in the locus coeruleus contain norepinephrine.

When low doses of these drugs are given to normal subjects, decreases in motor activity and increases in attention are also observed, although the effects are more subtle, most likely due to a ceiling effect. Basically what this means is that when drugs used to treat ADHD are given to those whose DA/NE transmission is within the normal range in the prefrontal cortex, there is a possibility that these drugs can increase DA/NE transmission *above* the normal range, which results in increased motor activity, impaired executive function, etc. (**Fig. 3**).

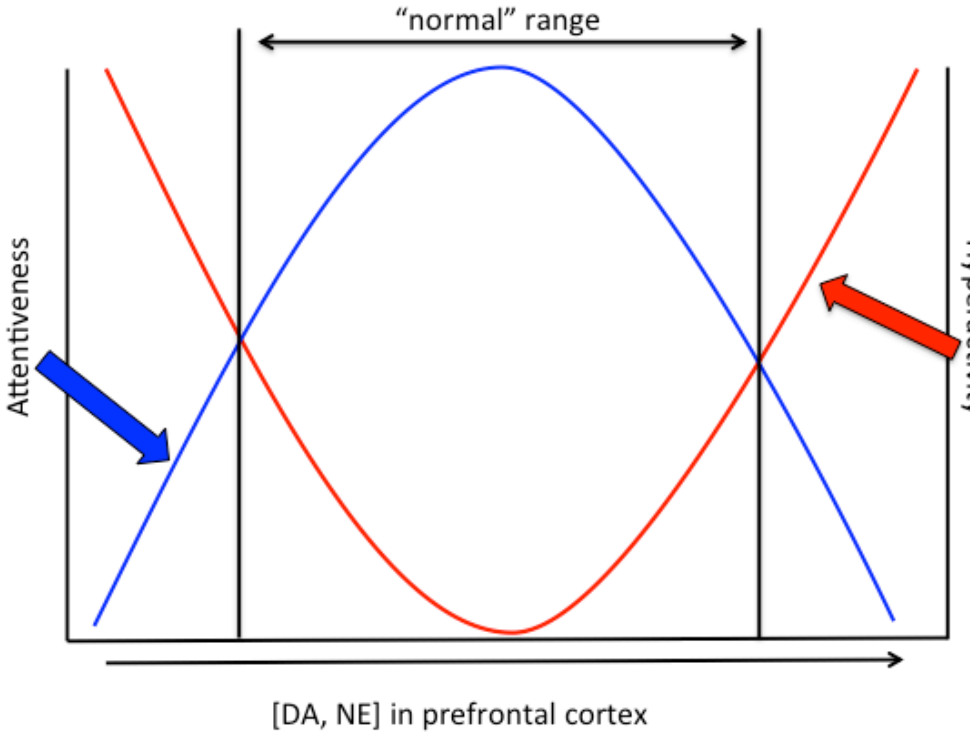


Fig. 3. Moderate levels of DA and NE in the prefrontal cortex are needed for optimal functioning of this region, as reflected in normal attentiveness and motor activity. If levels are DA and NE in the prefrontal cortex are too low, as is thought to occur with ADHD, then attentiveness will be impaired and hyperactivity increased. Interestingly, if DA and NE levels in the prefrontal cortex are too high, as is seen with high doses of stimulants, the behaviors that result share some similarities with the behaviors observed with ADHD.

It is important to note that atomoxetine is a *non-stimulant compound* as it selectively increases NE transmission, with little effect on DA release. As a result, atomoxetine has relatively less severe sympathomimetic effects and does not increase psychomotor activity. In addition, unlike methylphenidate and amphetamine, atomoxetine *does not induce DA release in the nucleus accumbens* (DA release in the nucleus accumbens is thought to contribute to the reinforcing effects of addictive substances), which contributes to its low potential for abuse and addiction. Atomoxetine's ability to treat the symptoms of ADHD lies in its ability to correct NE hypofunction in the prefrontal cortex. However, recent studies indicate that atomoxetine may not be as effective as the stimulant compounds in treating ADHD, possibly due to its lack of effect on the DA system.

Specific compounds: Stimulants

Methylphenidate

Methylphenidate is a stimulant that *blocks the reuptake of dopamine and norepinephrine* into the presynaptic neuron, resulting in increased levels of these neurotransmitters in the synapse. Most mixtures of methylphenidate are racemic, but the *d*-enantiomer is usually more pharmacologically active. The *d*-enantiomer of methylphenidate (dexmethylphenidate) is marketed as a separate compound, and may be given in half the dose of racemic methylphenidate. Methylphenidate is available in short-acting (3-5 h duration of action), intermediate-acting (3-8 h duration of action) and long-acting formulations (10-12 h duration of action). Methylphenidate, because of its propensity for diversion and abuse is a schedule II controlled substance.

Amphetamine

Amphetamine is a stimulant that *increases the release of DA and NE from the presynaptic neuron via reversal of the DA and NE transporters*, respectively. Amphetamine is available as *d*-enantiomer (dextroamphetamine) or as the racemic form (Adderall). A more recent formulation of amphetamine is the pro-drug lisdexamfetamine, which consists of *d*-amphetamine covalently bonded to *L*-lysine. Once the drug is ingested, it is converted to *d*-amphetamine and *L*-lysine via enzymatic hydrolysis. Lisdexamfetamine was designed to have less potential for abuse and toxicity than amphetamine. However, all amphetamine compounds are schedule II controlled substances.

Adverse effects of stimulants: Adverse effects include insomnia, anorexia, weight loss, motor or vocal tics and headaches. Infrequently, visual hallucinations and emotional lability occur with stimulant treatment, and growth retardation has been reported in some cases. Stimulants should be used with extreme caution in those with a history of mania, psychosis or drug/alcohol dependence. Stimulants should not be administered with other sympathomimetic compounds in order to prevent increased blood pressure and heart rate, or with monoamine oxidase inhibitors, in order to prevent a hypertensive crisis. Stimulants should not be taken with phenobarbital, phenytoin, or tricyclic antidepressants, as stimulants inhibit the metabolism of these compounds, leading to increased side effects/toxicity. Finally, because stimulants increase α-adrenergic receptor activation (and thus lead to pupillary dilation), they should not be used in closed-angle glaucoma.

Specific compounds: Non-stimulants

Atomoxetine

Atomoxetine is a non-stimulant compound that inhibits the reuptake of NE, and unlike methylphenidate and amphetamine, is not a controlled substance. Adverse effects of atomoxetine include abdominal pain, decreased appetite, vomiting, nausea, diarrhea, dizziness and somnolence. In addition, mean height and weight percentiles declined in children treated with atomoxetine, although this effect was reversed with discontinuation of the drug. Monoamine oxidase inhibitors and atomoxetine should not be administered together or within 2 weeks of each other, in order to prevent severe and possibly fatal hypertensive crisis. Atomoxetine is metabolized by the CYP2D6 isoenzyme and the half-life of atomoxetine may be increased if co-administered with the potent CYP2D6 inhibitors paroxetine and fluoxetine. There is little evidence that atomoxetine is as effective or well-tolerated as methylphenidate, but may be best for patients that cannot tolerate or don't respond to stimulants, or for those who do not want to take, or have their children take a controlled substance for their ADHD.

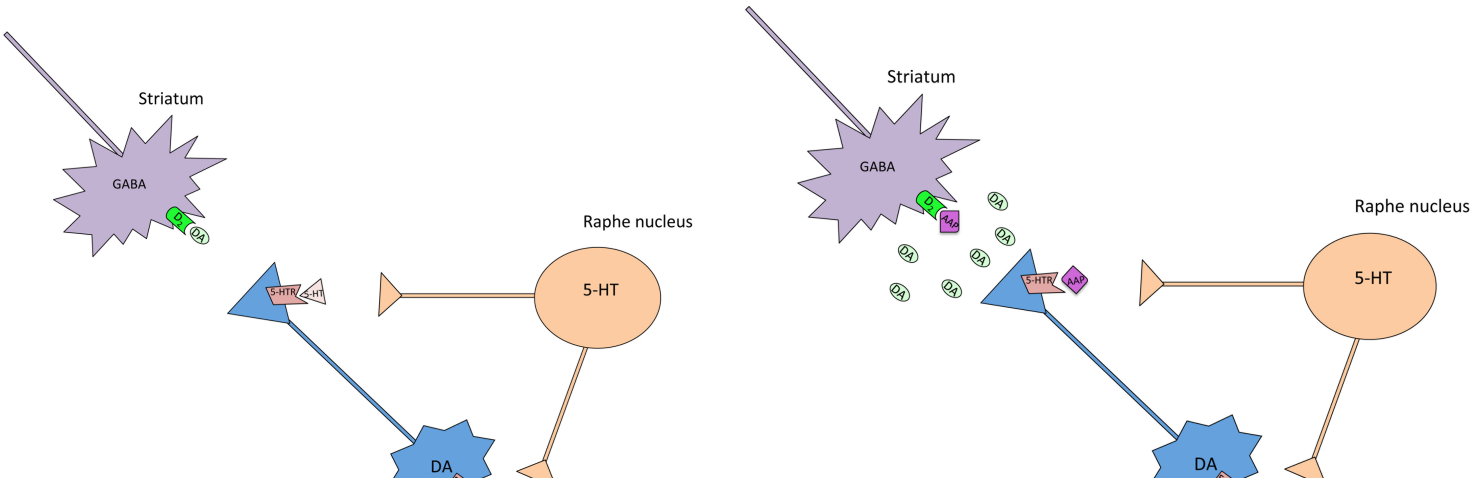
Atypical antipsychotics: interactions between the DA and Serotonin (5-HT) systems (Module 3)

Atypical antipsychotics are 5-HT Receptor-DA Receptor Antagonists. Atypical antipsychotics can bind to and block DA D_2 receptors, but are more potent antagonists of 5-HT_{2A} than D_2 receptors. Blockade of 5-HT_{2A} receptors may differentially modulate the activity of DA neurons in the nigrostriatal, mesolimbic and mesocortical pathways. It is this modulation of the DA system by the 5-HT system that may underlie the ability of these compounds to treat both the positive and negative symptoms of schizophrenia. Most importantly, this interaction between the DA and 5-HT systems reduces the occurrence of extrapyramidal side effects (EPS), as compared to traditional antipsychotics. Please note that aripiprazole is a *DA D_2 partial agonist*. Because of it's partial agonism of D_2 receptors, in the presence of endogenous DA, aripiprazole acts as a D_2 receptor *antagonist*. Also, a new atypical antipsychotic, *asenapine*, has recently been approved for treatment of schizophrenia and mania associated with bipolar disorder, and is available in a sublingual tablet formulation.

Atypical antipsychotics dissociate rapidly from DA D_2 receptors. The ability of atypical antipsychotics to rapidly dissociate from DA D_2 receptors may contribute to the reduced extrapyramidal effects observed with these compounds. Like typical antipsychotics, atypical antipsychotics block the D_2 receptor, but have a lower affinity for this receptor than the typical antipsychotics, due to the ability of atypical antipsychotics to rapidly dissociate from the D_2 receptor following binding. This means that when dopamine is released from nigrostriatal neurons during the initiation of voluntary movement, it can gain access to striatal D_2 receptors in a timely manner Remember, activation of inhibitory D_2 receptors results in decreased activation of the indirect pathway, relative to the direct pathway, allowing movement to occur.

For the most part, the typical antipsychotic drugs have slower dissociation rates, which means that DA cannot readily access the D_2 receptor. As a result, there is a lag between the time that DA is released from nigrostriatal nerve terminals and the time it can occupy the D_2 receptor, which allows ample opportunity for DA to be cleared from the synapse by the DA transporter before it can bind to D_2 receptors. The resulting decrease in DA interaction with D_2 receptors can cause a Parkinson's-like syndrome. In addition to their lower incidence of acute movement disorders, atypical antipsychotics may prove to have a lower incidence of late-onset movement disorders, such as tardive dyskinesia.

5-HT_{2A} receptor blockade, modulation of nigrostriatal DA neurons and extrapyramidal side effects. The decrease in the acute-onset extrapyramidal symptoms associated with the atypical antipsychotics also may be due to the unique regulatory effect of 5-HT_{2A} receptors on DA release from nigrostriatal neurons (**Fig. 4A**). The dopamine neurons of the substantia nigra pars compacta (which give rise to the nigrostriatal pathway) express 5-HT_{2A} receptors on their dendrites/soma and axon terminals (where they serve as *heteroceptors*). Serotonergic neurons, whose cell bodies lie in the raphe nucleus innervate the neurons of the substantia nigra pars



compacta. When 5-HT is released from the neurons of the raphe nucleus, 5-HT_{2A} receptors on nigrostriatal neurons are activated, which inhibits DA release in the caudate putamen. This goes on to some degree constantly in this pathway. When a patient is given an atypical antipsychotic, which acts as an antagonist at the 5-HT_{2A} receptor, the tonic inhibitory effect of 5-HT is blocked, causing more DA to be released from nigrostriatal neurons (**Fig. 4B**). When this happens, more DA is available to compete with the atypical antipsychotic agent that is bound to DA D_2 receptors in the caudate putamen. Since more DA will be available to bind to D_2 receptors in the striatum, there will be a reduction in the degree of DA D_2 receptor blockade by the atypical antipsychotic, which will prevent the Parkinson's-like effect that would normally be expected when a strong D_2 receptor antagonist, with relatively with less 5-HT_{2A} antagonist activity is administered (e.g., typical antipsychotics). In addition, blockade of 5-HT_{2A} receptors on GABAergic neurons in the globus pallidus may also counteract the inhibition of movement induced by D_2 receptor antagonism, also reducing the risk of EPS. Atypical antipsychotics can also antagonize inhibitory 5-HT_{1A} receptors located presynaptically on nigrostriatal neurons, which will also augment DA release.

5-HT_{2A} receptor blockade and alleviation of the positive and negative symptoms of schizophrenia. One advantage associated with the atypical antipsychotics is there may be improved efficacy against both the positive and negative symptoms of schizophrenia, compared to the traditional typical antipsychotics, which are effective in alleviating the positive symptoms of schizophrenia, with limited effect on the negative symptoms. The ability of the atypical antipsychotics to alleviate both negative and positive symptoms may be due modulation of DA activity in the mesocortical and mesolimbic pathways by 5-HT_{2A} receptors (**Fig 5**). The mesocortical pathway refers to the dopaminergic neurons that are located in the ventral tegmental area, and project to the frontal cortex, while the mesolimbic pathway refers to the dopaminergic neurons that are located in the ventral tegmental area and project to the nucleus accumbens and other limbic structures. It is thought that *decreased* dopaminergic activity of the mesocortical system is responsible for the negative symptoms of schizophrenia. 5-HT_{2A} antagonists may increase dopaminergic activity in the mesocortical projections, which is potentiated by the blockade of inhibitory D_2 autoreceptors located presynaptically on dopaminergic mesocortical nerve terminals. On the other hand, *increased* dopaminergic activity of the mesolimbic system may underlie the positive symptoms of schizophrenia. 5-HT_{2A} antagonists may decrease dopaminergic output from the mesolimbic system, which augments the D_2 antagonist effects of the atypical antipsychotics, resulting in an alleviation of positive symptoms.

Cariprazine (*Vraylar*) was approved for treatment of schizophrenia, as well as acute mania and bipolar I disorder in 2015. Cariprazine is a partial agonist at DA D_2 and 5-HT_{1A} receptors, and a full antagonist at 5-HT_{2A} receptors. Cariprazine also binds with high affinity to the DA D_3 receptor, which may modulate mood, although the mechanism for this effect is not clear. Cariprazine is metabolized mainly by CYP3A4, and is long-acting, as it is broken down into

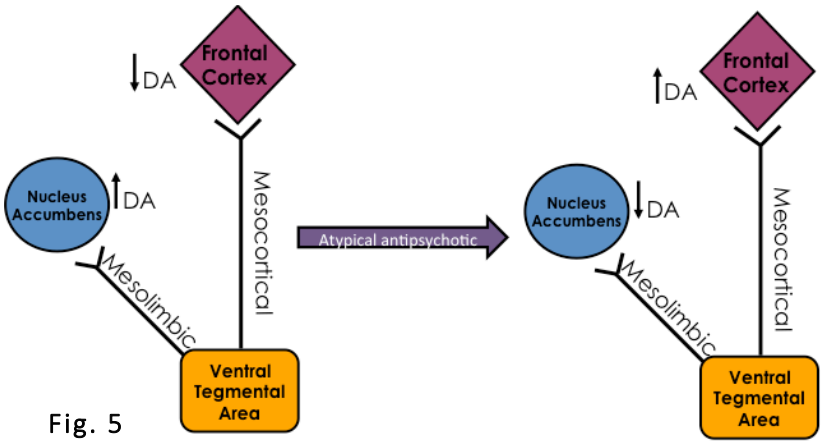


Fig. 5

Blockade of 5-HT_{2A} receptors is thought contribute to the reversal of DA overactivity In the mesolimbic system, and the enhancement of DA release in the mesocortical system.

to two active metabolites, desmethylcariprazine and didesmethylcariprazine. Cariprazine should not be used with other drugs that induce CYP3A4 activity, as this will reduce the efficacy of cariprazine. Cariprazine side effects include akathisia, dyspepsia, vomiting, somnolence and restlessness. Cariprazine appears to have mild metabolic effects, and may have some adverse extrapyramidal symptoms.

Hypnotics (Module 3)

Intermezzo

The FDA has recently approved *Intermezzo*, a low-dose sublingual tablet formulation of the benzodiazepine receptor agonist, zolpidem. Unlike other oral formulations of zolpidem, which are labeled for use only at bedtime, intermezzo can be used to treat insomnia due to middle-of-the-night awakening. Intermezzo reaches therapeutic levels in the plasma at approximately 20 minutes after administration and these levels may be maintained for up to four hours. The half-life of intermezzo is about 2.4 hours, and by 12h the compound is no longer detectable in the plasma. The adverse effects of intermezzo are similar to those seen with oral zolpidem formulations: somnolence, anterograde amnesia, tolerance and potential for abuse. Intermezzo or any other formulations of zolpidem are not recommended for use during pregnancy.

Suvorexant

The FDA has recently approved suvorexant (Belsomra), an orexin receptor antagonist for the treatment of sleep-onset and sleep-maintenance insomnia. During wakefulness, orexin neurons are active, and are quiescent during sleep. Activation of orexin receptors promotes wakefulness, so blockade of orexin receptors will promote sleep. The most common side effects of suvorexant treatment are next-day somnolence, and next-day impairment of activities that require mental alertness and motor coordination. Discontinuation of suvorexant does not appear to result in rebound insomnia or withdrawal

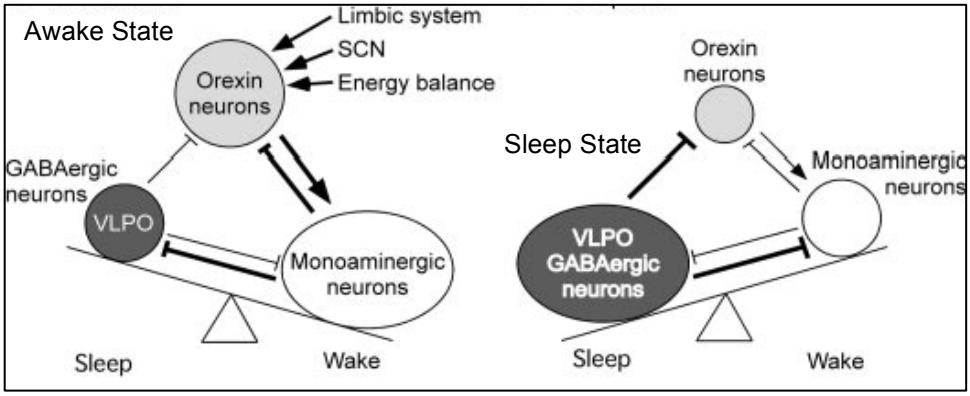


Fig. 6. During the awake state, orexin neurons in the hypothalamus are activated, and through the binding of orexin to orexin receptors, increases the activity of wake-active neurons in the brain stem that contain monoamines (e.g., serotonin, histamine). During wakefulness, these monoaminergic wake-active neurons also inhibit sleep-active GABA neurons in the ventrolateral preoptic (VLPO) area in the hypothalamus. During the sleep state, the orexin neurons are inhibited by the sleep-active GABA neurons in the VLPO, which reduces activation of wake-active monoaminergic neurons. VLPO neurons also directly inhibit wake-active monoaminergic neurons. Suvorexant works by blocking orexin receptors on wake-active neurons during, thereby preventing the activation of wake-active neurons by orexin, which promotes

symptoms. Caution should be taken when prescribing suvorexant to patients with compromised respiratory function or chronic obstructive pulmonary disorder, or those who may be pregnant, as suvorexant has not been studied in these populations. Suvorexant is metabolized by CYP3A4, and therefore, should not be co-administered with compounds that inhibit CYP3A4 (e.g., clarithromycin) or induce CYP3A4 (e.g., carbamazepine), as these compounds will respectively increase or decrease the half-life of suvorexant. Caution should also be exercised if the patient is also taking digoxin, as suvorexant can inhibit the breakdown of digoxin the P-glycoprotein. As with other sedative and hypnotic drugs, suvorexant should not be taken with other drugs used to treat insomnia, and it should not be taken with other drugs that depress the CNS or ethanol, as the sedative and CNS-depressant effects may be additive.

Valerian Root

Valerian root is an herbal medication that is thought to possess sedative, hypnotic and to a lesser extent, anxiolytic properties. Valerian root is composed of many different chemical compounds, including GABA. Several studies have shown that valerian may be effective in treating insomnia by reducing latency to sleep; however, several studies have also shown that valerian does not reduce the latency to sleep. Valerian appears to have few adverse effects, and should not be taken concomitantly with ethanol.

Drugs for migraine (Module 4)

Migraine headaches are thought to be due to the release of vasodilating peptides (such as substance P and calcitonin gene-related peptide) onto cranial nerves (such as the trigeminal nerve) and blood vessels, both intracranially and extracranially. Perivascular edema may occur due to the extravasation of plasma and proteins, leading to the stretching of the dura and nociceptive nerve endings within the dura. 5-$HT_{1B}/_{1D}$ receptors are located presynaptically on trigeminal nerve endings and cerebral/meningeal vessels, and since these receptors are inhibitory, their activation may inhibit the release of vasodilating peptides. Activation of 5-$HT_{1B}/_{1D}$ receptors can also induce vasoconstriction. Several drugs that are used to treat migraine have activity at 5-$HT_{1B}/_{1D}$ receptors.

Triptans

Triptans are 5-$HT_{1B}/_{1D}$ agonists and are often the drug of choice for moderate-to-severe migraine headaches. The use of a triptan early in a migraine attack, when the pain is still mild-to-moderate has also been shown to improve the treatment outcome. *Sumatriptan* is one of the more popular tritpans and is available in oral, nasal aerosol, injectable and transdermal patch formulations. The non-oral formulations may be of particular benefit to those who suffer from nausea and vomiting with their migraine headaches; these formulations also have a more rapid onset of action as compared to the oral formulations. A fixed formulation containing sumatriptan and the NSAID naproxen sodium (*Treximet*) is also available and appears to provide better pain relief than either agent taken alone for those with moderate-to-severe migraine. In general, there is a 20-40% of recurrence of migraine pain within 24h of taking a triptan; however, recurrences typically respond to a second dose of the triptan.

Adverse of effects of triptans include tingling, dizziness, drowsiness and fatigue. In rare instances, myocardial infarction, angina, cardiac arrhythmia, or stroke have occurred with triptan therapy. Triptans, which have some vasoconstrictive properties are contraindicated in patients that have coronary, cerebrovascular or any other arterial disease, and should be used with caution in those patients with risk factors for vascular disease (e.g., diabetes). Triptans should not be used within 24h of another triptan or ergot compound (see below), as the vasoconstriction caused by these compounds is additive. Since monoamine oxidase inhibitors (MAOIs) increase the serum concentration of sumatriptan, MOAIs and sumatriptan should not be used within two weeks of one another. Serotonin syndrome has been reported with the concurrent use of selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). In general, triptans are classified as inducing fetal/embryonic toxicity in animals; however, sumatriptan has been used for a number of years in pregnant women and does not appear to be associated with an increased risk of birth defects.

Ergots

Ergotamine is a nonspecific serotonin agonist and possesses vasoconstrictive properties. Ergotamine has been used for years to treat moderate-to-severe migraine headaches, and is available alone in sublingual tables or in combination with caffeine in an oral formulation. Oral

ergotamine plus caffeine appears to be less effective than a triptan for the treatment of acute migraine.

Adverse effects of ergotamine include nausea and vomiting, but these effects can be prevented by the concurrent administration of an antiemetic. Vascular occlusion is a rare adverse effect of ergotamine, and ergots are contraindicated in patients with uncontrolled hypertension or arterial disease. Triptans, beta blockers, dopamine, nicotine or CYP3A4 inhibitors can all potentiate the effects of ergots. Ergots and triptans should not be taken within 24h of each other.

Beta blockers

Beta blockers are commonly used for continuous prophylaxis of migraine headache. The only FDA-approved beta blockers for migraine prophylaxis are *propranolol* and *timolol*. These compounds can cause fatigue and orthostatic hypertension, and should not be used in patients with decompensated heart failure. Beta blockers, due to their antagonism of β_2 receptors are contraindicated in patients with asthma. Interestingly, patients with migraine often have comorbid depression, and beta blockers seem to worsen depressive symptoms.

Anti-epileptic drugs

Valproate and *topiramate* are FDA-approved for migraine headache prophylaxis. Recent studies indicate that about 50% of patients treated with these drugs achieve >50% reduction in migraine headache frequency. Adverse effects of valproate include nausea, fatigue, tremor, weight gain, hair loss, lipid abnormalities, hyperinsulinemia, hirsutism and menstrual disturbances. Rarer adverse effects include acute hepatic failure and pancreatitis. Valproate is not recommended for use during pregnancy, as lower IQ scores have been reported in those who were exposed to valproate *in utero*. Topiramate often causes paresthesias, fatigue, cognitive and language impairment, taste perversion and weight loss. In rare cases, topiramate can cause secondary narrow angle glaucoma, oligohydrosis (diminished ability to sweat, which can result in hyperthermia), nephrolithiasis (kidney stones) and metabolic acidosis. Topiramate has been associated with an increased risk of cleft lip and cleft palate and is not recommended for use during pregnancy.

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Week 5: Case 1A: Autism (development)

A 4-year-old child is brought by his parents to the pediatrician:

CC: Abnormal behavior

HPI: Most recently the patient was enrolled in preschool, and he has not adjusted well, crying and having tantrums during the first hour of school each day. He usually calms down but does not interact with the other children. His teacher indicated that the patient does not follow directions and does not look at her when she speaks to him. The patient did not speak his first word until he was 2, and as an infant, he rarely smiled, did not make eye contact and did not enjoyed being held. The parents also relate that the patient uses his toys inappropriately and engages in a single, repetitive movements for hours on in.

PMH: No major illnesses and up to date on his vaccinations. No allergies or surgeries

Social History: Patient is an only child, parents separated with impending divorce.

Family History: Both parents alive and well, no siblings and no family history of developmental delay.

ROS: Negative

Physical Exam: The patient is awake and alert. He has a vocabulary of 10 words. He does not use more than 2 words in a row. When the pediatrician picks the patient up to put him on the exam table, he stiffens and pushes himself away from the examiner. He does not respond to requests made by the pediatrician, nor does he make eye contact.
Patient appears to have normal vision, extraocular eye movements, hearing and normal motor, sensory and reflex examination.

Case goals: To facilitate discussion of normal development, intellectual disability and autistic spectrum disorders

Suggested Topics:

1. Discuss developmental theories and apply these theories to patients and families in subsequent cases (Topic 1)
2. Discuss the normal stages of development and relate them to this patient (Topic 1)
3. Explain how mirror neurons may play a role in social interaction (Topic 4; objectives 8 and 9)
4. Consider the impact of divorce on development (Topic 1)

Week 5: Case 2B Emotion (limbic system)

26 -year-old female brought to the ER after being attacked.

CC: Facial lacerations

HPI: Patient was walking alone in a dark alley when she was attacked by an unknown assailant. Apparently this was not an unusual activity for this patient.

PMH: No major illnesses, no surgeries, no allergies.

Social History: Teacher, unmarried, no substance abuse

Family History: Parents and one sibling alive and well, no family history of neurological disorders

ROS: Negative

Physical Exam: BP 104/68, HR 72, RR 14, T 36.4 C
Well-developed well-nourished female in no distress. Physical exam showing multiple facial lacerations and no other abnormalities
On neurological exam she was awake alert with normal orientation, concentration, language and memory. The patient was given a series of photographs depicting facial expressions. The patient recognizes all facial expressions except for those depicting fear. No cranial nerve motor sensory or reflex abnormalities.

Data: MRI brain scan demonstrates bilateral calcification of the anterior medial temporal lobes

Case goals: To facilitate the discussion of the limbic system and its role in the expression of emotion

Suggested Topics:

1. Define personality and the continuum from normality to pathology (Topic 2)
2. Identify the brain region that is most likely affected in this patient (Topic 3).
3. Describe the function of the limbic system (Topic 3).
4. Discuss the limbic loop and how it relates to the development of emotional responses (Topic 3)

Week 5: Case 3C Lesions in Motor Pathways (decerebrate/decorticate rigidity)

A 24-year-old man is brought to the emergency room

HPI: The patient was driving to dinner with his girlfriend and was hit by a truck that ran a red light. He had no loss of consciousness and instantly noticed pain in his thoracic area with inability to move or feel his legs.

PMH: No major illnesses, on no medications no allergies and no surgeries

Social History: Engineer, without substance abuse, married

ROS: Negative

Physical Exam: BP 128/82; HR 92; RR 16; T 36.8 C
Well-developed well-nourished man in moderate discomfort. Physical exam showed tenderness to mild percussion over the mid thoracic area.
On neurological exam no mental status or cranial nerve abnormalities. Good strength in his upper extremities. He has no movement in either lower extremity. Fasciculations are noted on his torso. He has diminished pain and temperature sensation in both lower extremities and the lower portion of his and his torso. He had normal vibration, light touch and position sense in his upper and lower extremities. In his lower extremities he had increased reflexes, increased tone and bilateral Babinski responses.

Case goals: Using your knowledge of motor pathways, identify the area(s) affected in this patient and explain how damage to these areas lead to the symptoms observed.

Suggested Topics:

1. Lesions of the motor pathways (Topic 6)
2. Muscle receptors and Spinal Reflexes (Topic 8)
3. Centrally acting spasmolytics and skeletal muscle relaxants (Topic 9)
4. Review Topic 17 Organization and control of movement **Module 1**

Week 5: Case 4C Lesions in Motor Pathways (decerebrate/decorticate rigidity)

A 22 year old female in the emergency room waiting area has a sudden loss of consciousness.

HPI: Patient was a passenger in the same vehicle as case 3. She had a brief loss of consciousness at the time of the accident but refused treatment and was waiting to see her boy friend in the emergency department reception area. She had a sudden loss of consciousness and was moved back to the treatment area.

Staff was unable to get a past medical history, social history family history or review of systems.

Physical Exam: BP 140/80; HR 60; RR 12; T 36.0
Patient has a moderate contusion in the right temporoparietal area. She is comatose with fixed dilated pupils. She has extended upper and lower extremities bilaterally, with spasticity in all 4 extremities and positive Babinski reflexes.

Case goals: Using your knowledge of motor pathways, identify the area(s) affected in this patient and explain how damage to these areas lead to the symptoms observed.

Suggested Topics:

1. Lesions of the motor pathways (Topic 6)
2. Muscle receptors and Spinal Reflexes (Topic 8)
3. Centrally acting spasmolytics and skeletal muscle relaxants (Topic 9)
4. Review Topic 24: Cerebral circulation and stroke in **Module 1**

Week 5: Case 5D Association cortices (aphasias)

A 64-year-old male is brought to the ER by his daughter:

CC: Difficulty speaking

HPI: Patient had a sudden onset early in the evening of problems speaking. He is right-handed. He had no prior similar problem.

PMH: Hypertension, dyslipidemia and type 2 diabetes.

Family History: Mother died of stroke at age 60, father died of pneumonia in his 80s.

Social History: One pack per day smoking history, 2-3 drinks per night and no drug use. Truck driver

No allergies

Surgical History: Previous appendectomy and cholecystectomy

Medications: Hydrochlorothiazide, lisinopril, metformin, atorvastatin

ROS: Occasional headaches, nocturia, moderate joint pain

Physical Exam: BP 178/104; HR 92; RR 16; T 36.4 C; BMI 32
Overweight man in no acute distress. Normal HEENT exam, no bruits, clear lungs, no heart murmurs, negative abdominal exam, full pulses and no peripheral edema.
He was awake and alert but had unintelligible speech. He was able to follow written and spoken commands. He mumbled with a hesitant fashion and appeared frustrated when asked questions to which he could not respond. He was able to read and understand written questions but was not able to write. He had slight weakness on the lower portion of his right face.

Case goals: To facilitate discussion of language and disorders of language

Suggested Topics:

1. Language and aphasias (Topic 5)
2. Review Topic 24: Cerebral circulation and stroke in **Module 1**

Week 6: Case 6A Neural plasticity and neurogenesis

A 4-year-old female recently adopted from China, is brought to the pediatrician for a physical.

CC: Eyes appear crossed

HPI: Adoptive parents had noticed problems with patient's eyes since bringing her home. They know no details about the onset.

PMH, Social History, Family History, ROS: Unknown

Physical Exam: BP 96/54; HR 92; RR 16;t 37.0
Well-developed well-nourished patient with no abnormalities on physical exam. No cataracts and no inflammation in and around her eyes on either side.
Patient was awake and alert was able to speak Chinese. She had equal pupils size and responses. She had full visual fields to threat. She was able to follow an object with her right eye when her left eye is covered, but cannot follow the object with her left eye when the right eye is covered. No other neurological deficits.

Patient was given a patch to wear over her right eye for 6 hours a day for the next 2 months

Case goals: To facilitate discussion of the concept of critical periods in neural development

Suggested Topics:

1. Neural plasticity and neurogenesis (Topic 10)

Week 6: Case 7B Cerebrovascular disease

57-year-old female brought to the emergency room

CC: Sudden headache followed by brief loss of consciousness.

HPI: One hour prior to presentation she noted sudden onset of the worst headache in her life. This was global. Shortly thereafter there was a brief loss of consciousness. For the last 2 weeks she has` been complaining of a moderate aching right-sided headache. Two days ago she noted that her right eye was droopy and when she woke up the morning of her presentation, she complained of double vision.

PMH: Hypertension poorly controlled

Medication: Hydrochlorothiazide, lisinopril, clonidine

Social History: 2 pack per day smoker, 1-2 alcoholic beverages per night no drug use, homemaker

Family History: Both parents with hypertension

ROS: Occasional headaches, the recently noted double vision, frequent productive cough and urinary frequency

Physical Exam: BP 190/108: HR 92: RRR 14:T 36.8 C

Well-developed well-nourished female in obvious discomfort. She had moderate nuchal rigidity. Negative cardiopulmonary exam and normal abdominal exam. Full pulses and no edema. She was awake and alert, normal orientation memory and language. On cranial nerve exam she had ptosis on the right, a right pupil larger than the left and poorly responsive to light directly and consensually, the right eye was down and out. There were no other neurological deficits.

Case goals: To facilitate discussion of the pathology of cerebrovascular disease and resulting brain injury

Suggested Topics:

1. Cerebrovascular disease/ischemic brain injury (Topic 13)
2. Compare and contrast cerebral ischemic lesions and intracerebral hemorrhage. (Topic 13)
3. Review Topic 19: Cranial Nerves from **Module 1** to explain symptoms

Week 6: Case 8C Learning and memory

A 63-year-old male is brought to his family physician by his wife

CC: "He has to stop driving."

HPI: 3 years ago wife relates that patient developed mild memory problems for recent events. Within the past 9 months he has deteriorated to the point that he is no longer able to manage his family finances. At that point she had cautioned him against driving alone. The previous week she had repeated her admonition but he had angrily left home to drive to the neighborhood grocery store. When he did not return after 5 hours she became worried and phoned the police. He had been stopped in a neighboring community for running a stop sign and arrested since he appeared very confused. He could give no reason for being 30 miles from home. He later claimed "Someone must have tampered with my car." He often gets lost by walking around his neighborhood, where he has resided for the past 30 years. Last year he was given a prescription for scopolamine by his primary care physician to prevent motion sickness while on a cruise with his family. Wife indicates that after taking several doses of the scopolamine, the patient began having visual hallucinations and shouting incoherently, but the symptoms resolved after he stopped using the medication.

PMH: Elevated cholesterol no other major illnesses

Medication: Atorvastatin

Surgical History: Appendectomy, cataract removal, no allergies.

Social History: Retired insurance salesman, no smoking, occasional alcohol but none in the last year, no drug use.

Family History: Mother had early onset memory problems

ROS: Occasional joint pain otherwise negative

Physical Exam: She 132/84; HR 72; RR 14; T 36.8 C
Well-developed well-nourished man in no distress. Normal detail physical exam.
On mental status exam he was oriented to person and place but not to date. He knew the names of his wife and children but not of his grandchildren. He could recall neither his phone number nor street address. He was unable to count backwards from 100 by 7's, 40 by 4's or 20 by 2's. His remote memory was good but he was unable to recall any of 3 objects the physician had given him and instructed him to remember after 5 minutes. Insight and judgment were very limited. There was no homicidal or suicidal ideation or evidence of depression. Cranial nerve, motor, sensory, and reflex examinations were all normal.

Data: He had an unremarkable CBC and chemistry profile, normal B12 level, thyroid studies and negative RPR. MRI of the brain revealed mild to moderate cortical atrophy and corresponding ventricular dilatation (hydrocephalus ex vacuo).

Image 2 is a brain tissue specimen obtained postmortem from a patient with similar clinical findings.

Image 1

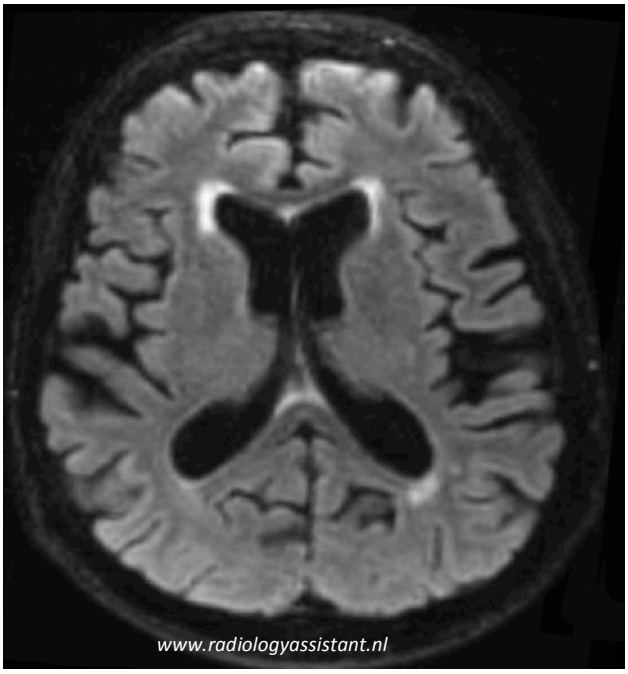
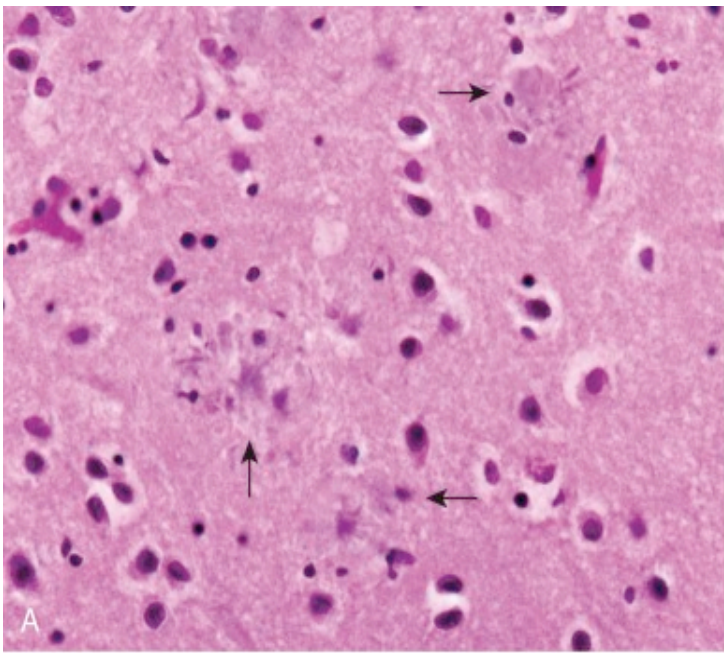


Image 2



Case goals: To facilitate the discussion of learning, memory and the pathophysiology of disorders of memory

Suggested Topics:

1. Discuss the application of learning theory. Learning and Memory (Topic 11)
2. Define LTP and the cellular changes associated the development of LTP in the hippocampus (Topic 11)
3. Discuss the clinical and pathologic features associated with the most common types of dementia (Topic 12)
4. Define delirium and contrast with dementia (Topic 12)
5. Discuss the social, psychological and pharmacological treatment of dementia (Topic 12)
6. Discuss the special concerns of prescribing drugs for the elderly (Topic 14)
7. Discuss competence and the ability of the patient to make informed decisions (Topic 15)

Week 7: Case 9A Eating disorders

A 20-year-old single female presents to the hospital eating disorders clinic

CC: "I've had lots of headaches lately."

HPI: Patient had recently immigrated to United States from South Africa with her family to do missionary work. She had been noticing frequent headaches for the last several months and chronic fatigue. She saw an internal medicine physician who was unable to find any medical explanation and because of concern about her extremely low weight, the physician referred the patient to the clinic.

PMH: No major medical illnesses

Medication: No prescription drugs or OTC drug

Social History: She does not use tobacco alcohol or illicit drugs. She is not sexually active

No surgeries and no allergies

ROS: Fatigue for several months, 10 KG (22 pounds) weight loss in the past 3 months. She has diminished appetite. One-month history of dull aching global headaches. She missed her last menstrual period otherwise negative comprehensive review of systems.

Physical Examination: BP 95/50; HR 90; RR 14; T 36.7 C HEIGHT 155 CM (61"); WEIGHT 35.5 KG (78 lbs) BMI 14.7
Well-developed cachectic female in mild distress.

HEENT: Normocephalic; atraumatic; mild symmetrical temporal wasting; fine lanugo on face noted (See image 1 below). Thin scalp hair. Visual review of the oral cavity is shown in image 2.
Normal cardiopulmonary and abdominal exam. Warm and dry extremities with normal pulses. Skin was dry.
No neurological deficits other than mild muscle wasting.

Laboratory Findings:	**Patient**	**Normals (reference**

values)

WBC count, Total	4150/mm^3	4500 - 11,000/mm^3
Hgb	11.1 g/dL	12.0 - 16.0 g/dL
Hct	33%	36% - 46%
Platelet count	166,000/mm^3	150,000 - 400,000/mm^3
Serum Chemistries:		
Sodium	138 mEq/L	135 - 147 mEq/L
Potassium	3.8 mEq/L	3.5 - .0 mEq/L
Chloride	96 mEq/L	96 - 105 mEq/L
Bicarbonate	25 mEq/L	22 - 26 mEq/L
Glucose	42 mg/dL	70 - 110 mg/dL
Creatinine	0.6 mg/dL	0.6 – 1.2 mg/dL
Urea Nitrogen	10 mg/dL	7 – 18 mg/dL
Total Protein	5.6 g/dL	6.0 – 7.8 g/dL
Albumin	2.8 g/dL	3.5 – 5.5 g/dL
Alkaline phosphatase	30 U/L	20 – 70 U/L
AST	25 U/L	8 – 20 U/L
ALT	30 U/L	8 – 20 U/L
Total bilirubin	0.2 mg/dL	0.1 – 1.0 mg/dL

Psychiatric Evaluation:

Upon presentation for psychiatric evaluation, Ms. Gaspard is cooperative and pleasant. She expressed concern about her low weight and denied fear of weight gain or body image disturbance: “I know I need to gain weight. I’m too skinny,” she said. Ms. Gaspard reported that she had weighed 97 pounds prior to moving to the United States and said she felt “embarrassed” when her family members and even strangers told her she had grown too thin. Notably, everyone else in her U.S.-dwelling extended family is either of normal weight or overweight.

Despite her apparent motivation to correct her malnutrition, Ms. Gaspard's dietary recall revealed that she is consuming only 600 calories per day. The day before the evaluation, for example, she had eaten only a small bowl of macaroni pasta, a plate of steamed broccoli, and a cup of black beans. Her fluid intake is also quite limited, typically consisting of only two or three glasses of water daily.

Ms. Gaspard provided multiple reasons for her poor intake. The first is lack of appetite: "My brain doesn't even signal that I'm hungry," she said. "I have no desire to eat throughout the whole day." The second is postprandial bloating and nausea: "I just feel so uncomfortable after eating." The third is the limited choice of foods permitted by her religion, which advocates a vegetarian diet. "My body is not really my own. It is a temple of God," she explained. The fourth reason is that her preferred sources of vegetarian protein (e.g., tofu, processed meat substitutes) were not affordable within her meager budget. Ms. Gaspard had not completed high school and made very little money working at a secretarial job at her church.

Ms. Gaspard denied any other symptoms of disordered eating, including binge eating, purging, or other behaviors intended to promote weight loss. However, with regard to exercise, she reported that she walked for approximately 3–4 hours per day. She denied that her activity is motivated by a desire to burn calories. Instead, Ms. Gaspard stated that because she did not have a car and disliked waiting for the bus, she traveled on foot to all work and leisure activities.

Ms. Gaspard reported no other notable psychiatric symptoms apart from her inadequate food intake and excessive physical activity. She appeared euthymic and did not report any symptoms of depression. She denied using alcohol or illicit drugs. She noted that her concentration is poor but expressed hope that a herbal supplement she had just begun taking would improve her memory. When queried about past treatment history, she reported that she had briefly seen a dietitian about a year earlier when her family began "nagging" her about her low weight, but she had not viewed the meetings as helpful.

Image 3

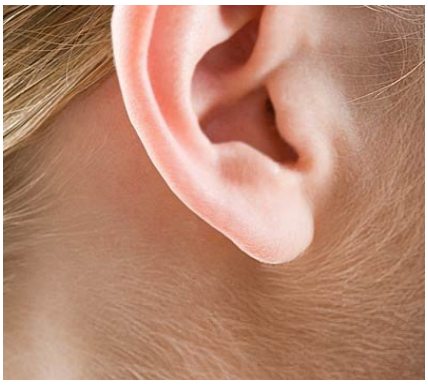
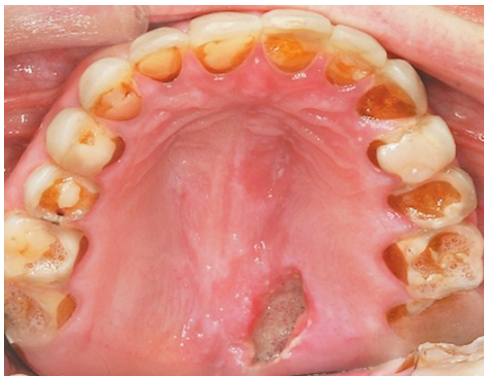


Image 4



Case goals: Discuss the diagnosis and treatment of eating disorders

Suggested Topics:

1. Compare and contrast various forms of eating disorders (Topic 16)
2. Discuss the behavioral and pharmacological treatment of eating disorders (Topic 16)

Week 7: Case 10B Cerebellum

10-year-old male is referred to the pediatric neurologist

CC: Headaches, double vision and unsteadiness.

HPI: 2 months ago patient began complaining of headaches in the frontal and parietal areas. These headaches were intensified by coughing, sneezing or bending forward, and sometimes accompanied by vomiting. Over this period of time mother had noted he had a tendency to fall to the left side. When descending stairs or reading he complained of double vision. He feels tired most of the time.

PMH: No prior medical problems

Surgeries: None

Allergies: None

Social History: Patient in elementary school and prior to these complaints was doing well. No substance use

Family History: Both parents and 2 siblings alive and well

ROS: Negative other than HPI

Physical Exam: BP 100/60; HR 84; RR 14; T 36.2 C
Well-developed well-nourished male in no distress. He is awake and alert with normal speech and memory. On cranial nerve exam he has equally round and reactive pupils but bilateral papilledema. Visual fields are normal. The left eye is slightly higher than the right eye when he looks down. He has normal facial movement and sensation, normal gag reflex and tongue protrusion. On motor exam he has no paralysis but had a wide-based gait and difficulty standing on his left leg, which was not worsened by closing his eyes. There is an intention tremor in the left upper extremity and dysmetria in the left upper and lower extremities. Dysdiadochokinesia is present in the left hand. Sensation and reflexes are normal.

Case Goals: To facilitate discussion of the role of the cerebellum in coordination of movement and to explain the consequences of cerebellar lesion

Suggested Topics

1. Describe the cerebellar circuitry including inputs and outputs (Topic 17)
2. Discuss potential lesions of the cerebellum and their clinical presentation (Topic 17)
3. Review CNS tumors, Topic 38 in **Module 1**

Week 7: Case 11C Neurodegenerative diseases affecting the motor system

A 40-year-old male is brought to the psychiatrist by his distressed wife

CC: "Major change in behavior"

HPI: Over the past several months the patient's wife has noted that the patient has had a marked change in his behavior, resulting in several bitter arguments between the couple. The wife states he has become impulsive and sometimes distracted, and on several occasions and has forgotten to pick up their toddler at day care after work. Patient himself denies any problems other than forgetfulness which he attributes to stress at work. Wife has noted that he occasionally stumbles when walking and he had a recent fall at work.

PMH: No major illnesses and on no medication

Social History: Accountant, no smoking or drug use. Occasional alcohol beverage

Family History: Mother alive and well, father died in a motorcycle accident at age 29. He has a brother 6 years younger with no problems.

ROS: Negative

No allergies or surgeries

Physical Exam: BP 132/84; HR 74; RR 14; T 36.4 C
Well-developed well-nourished man in no distress. Normal orientation and language. Cranial nerves normal. On motor exam psychiatrist notices that the patient has occasional irregular jerking movements of his hands, head and neck, some of which he incorporates into what appears to be purposeful movement. When asked about these movements, he minimalizes the significance and states he has had them for a while without any change. He has no paralysis and normal sensory and reflex examination.

Case Goals: To facilitate discussion of neurodegenative motor disorders

Suggested Topics:

1. Discuss how the basal ganglia modulate movement (Topic 18)

2. Describe the pathophysiology associated with common diseases of the basal ganglia.(Topics 18, 19)
3. Discuss the pharmacotherapy for basal ganglia diseases (Topic 19)

Week 8: Case 12A Alcohol and drugs of abuse (limbic system)

A 19-year-old high school senior is brought to the ER post-MVA

CC: Bleeding from scalp

HPI: Patient had been in a local bar and while driving his car home was involved in a single vehicle accident colliding with a light post.

PMH: No major illnesses

On no prescribed medications and no allergies

Past Surgical History: Appendectomy

Social History: Patient admitted to minimal alcohol use and denied any drug use. He has been smoking 2 packs per day for 3 years.

Physical Exam: BP 140/88 HR 102; RR 16; T 36.6 C
Abrasion requiring suturing over his left eye. No other significant injuries. Normal cardiopulmonary and abdominal exams. Extremities demonstrates needle marks over arms bilaterally. Patient has noticeable alcohol on his breath. No neurological deficits.

Data: Normal baseline labs but urine drug screen positive for opiates, blood alcohol 0.24% (0.08 considered intoxicated)

Hospital Course: Though initially both patient and parents minimize any substance abuse, the patient's mother admits that she has discovered drug paraphernalia in his room and found him to be intoxicated on several occasions. She is particularly concerned that her son is headed for serious legal problems, despite her minimization of his substance abuse. The mother says, "He is just being a normal teenager. Besides I drink every day, and I am fine". After a strong confrontation, Freddie admits that his drug use has gotten out of control, and he could not resist the pressure of his friends. He indicates that he can stop using whenever he wants, but has not considered quitting, even though using cigarettes drugs and alcohol have become less pleasurable. He admits having suicidal thoughts on at least 2 occasions (e.g.,"I felt like running my car into a bridge"). He rationalizes his drug use by stating "It's in my blood, it's in my family."

Case Goals: To facilitate a discussion of drug abuse and dependency

Suggested Topics:

1. Describe the epidemiology, etiology and treatment of substance abuse (Topic 21)
2. Discuss the common drugs of abuse (Topic 21)

3. Consider the pharmacological and behavioral treatment for substance abuse (Topic 21)
4. Review the limbic reward pathway (Topic 3, objectives 7,8)

Week 8: Case 13B Personality disorders

A 23-year-old female admitted to the inpatient psychiatric service

CC: Suicide attempt

HPI: Patient was admitted after slashing her wrists. The lacerations are superficial and do not require stitches. Patient indicates that she is often depressed, but this only lasts "for a couple hours". She relates that her psychiatrist recently left for two week vacation, and expresses rage at him for "abandoning her". She also indicates that she has dozens of "mania's" lasting for a day or two, where she is edgy and energized and pulls all nighters. This is her fourth admission to the psychiatric unit, her previous hospital admissions occurred as a result of an overdose or slashing her wrists, and were precipitated by someone leaving her life, even if it was temporary. Patient also relates she is plagued by chronic feelings of emptiness.

PMH: No major illnesses

Medication: Sertraline

Social History: Unemployed hairdresser single, no alcohol, no tobacco and no illicit drug use.

No major surgeries, no allergies

ROS: Occasional headaches and constipation otherwise negative

Physical exam: BP 105/72; HR 78; RR 16; T 36.2 C
Mild lacerations on her wrists otherwise negative physical exam. No neurological deficits.

Case Goals: To facilitate the discussion of personality disorders

Suggested Topics:

1. Discuss the continuum from eccentric individuals to those that are pathologically ill (Topic 20)
2. Compare and contrast the common personality disorders (Topic 20)
3. Discuss possible treatment options (Topic 20)

Week 8: Case 14C Student abuse and impairment

Patrick Campbell is a fellow first-year medical student. He did well in Block 1, but has recently been turning up late to his morning classes. Patrick's appearance has become disheveled, and you notice that on several occasions after returning from lunch he smelled of alcohol. You have

heard that Patrick might be having some recent personal issues, but you do not know anything else about his situation. One day when you were sat next to him during an afternoon session and smelled alcohol, you kidded him about his "three martini lunch." He just glared, and when you asked if he was OK, he told you he was fine and to mind your own business. Patrick's behavior has become more irritable, and he has verbally accosted his professor and other students during class. Yesterday you heard him complain about "all the stupid exams" (a sentiment with which you and others do not entirely disagree) but his tone and failure to pass the most recent exam concerns you. Your reaction initially is to feel angry and dismissive. You also think that, since you don't know him that well, this isn't really your concern and others should intervene.

Case Goals:

1. Discuss what steps might be taken next to address this student's situation.
2. Discuss concerns that arise from this student's situation.

Block 2, Module 2

Facilitator guide for PBL cases

Week 5

Case 1A: Autism, development

The patient's symptoms--difficulty with social reciprocity, poor peer interaction, poor language development, repetitive and odd play--and history are consistent with a diagnosis of autism spectrum disorder (ASD). The diagnostic criteria for ASD include deficits in three domains: social-emotional reciprocity (the ability to read and to exhibit verbal and nonverbal behaviors in interacting with others), deficits in non-verbal communicative behaviors and deficits in developing, maintaining and understanding relationships. Patients with ASD may also exhibit **repetitive and stereotyped patterns of behavior,** including inflexible adherence to rules or stereotyped motor mannerisms (purposeless, repetitive movements and behavior such as spinning, toe-walking or hand flapping). They can also be persistently preoccupied with parts of objects.

There may also be a failure or difficulty in learning spoken language. In this case, Jimmy exhibits poor language development, as a normal 4-year old child should have a large vocabulary consisting of hundreds of words. A normal child should be easily able to use several words in a sentence, and the child's comprehension of words should be even better than his ability to use them. In cases where early autism is suspected, a full medical workup should always be scheduled to rule out hearing or vision difficulties that can result in poor language development.

The symptoms of ASD often go unrecognized until the child is placed in an environment with other children of a similar age. This lack of recognition of the problem is especially likely to occur in a family with no other children, where it is not possible to compare developmental milestones.

In *DSM-5* the previous diagnoses of autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified have been consolidated into ASD. The DSM-V also has indicators that identify the level of patients' intellectual or language impairments. The differences in presentation are now differentiated by severity specifiers. These severity specifiers include social communication impairments and repetitive patterns of behavior.

Some previous disorders that are now consolidated into ASD:

- **ASPERGER DISORDER:** This is old terminology for a type of ASD that describes individuals who display social impairment and restricted interests and behavior (stereotyped behavior) but have normal language and cognitive skills.
- **RETT DISORDER: This is old terminology for a type of ASD that describes individuals who show a type of** childhood developmental disorder of unknown etiology in which the patient develops progressive encephalopathy, loss of speech capacity, gait problems, stereotyped movements, microcephaly, and poor social interaction skills. The child must have shown normal development in early infancy, and only females are affected.

- **CHILDHOOD DISINTIGRATIVE DISORDER**: Old terminology for a type of ASD that describes individuals whose development progresses normally until approximately the age of 2, after which the individual loses previously acquired skills in two or more of the following areas: language, social responsiveness, bladder/bowel control, play, motor skills.

Boys are more often affected by ASD than girls by a three- to fivefold increased prevalence. The etiology of ASD is unknown, but a genetic etiology is likely. Family studies show a markedly increased incidence in monozygotic twins and a low risk in dizygotic twins. Elevated serum serotonin levels can be a clue to the neurochemical abnormality. Approximately 40% of children with autistic disorder are mentally retarded; however, some demonstrate unusual or extremely precocious abilities, the so-called islets of precocity. One such talent is the ability to perform extraordinary mathematical calculations although the child is cognitively impaired in other ways.

Magnetic resonance imaging (MRI) studies have shown that patients with autism demonstrate evidence of increased cortical thickness that may relate to abnormalities in cortical connectivity. Functional magnetic resonance imaging (fMRI) studies have shown less activation of the prefrontal regions indicating a dysfunction of the frontostriatal networks in patients with autism spectrum disorders. Other studies have demonstrated abnormalities in glutamate/glutamine physiology, particularly in the limbic areas. Clearly, ASD is a complex disorder with multiple dimensions of etiology.

Researchers and clinicians in the field have exhaustively reviewed and tested the role of childhood vaccinations in the development of ASD. A large meta-analysis of almost 15 million children looked at vaccine efficacy and safety. *The generally accepted conclusion is that there is* ***no association between childhood vaccinations*** *(or their preserving agents) in the development of autism.*

Although a child with schizophrenia can exhibit poor social functioning and affective withdrawal, the onset of childhood schizophrenia usually occurs later, there is a family history of schizophrenia, and the child is less impaired in the area of intellectual functioning. Children with obsessive-compulsive disorder (OCD) can display stereotypical behavior or perform rituals, but they have a more normal course of development otherwise. They also do not exhibit impairment in social interaction or communication. Mental retardation exhibit similar symptoms to ASD; however mentally retarded children generally do not exhibit restricted activities and interests or impairments in communication and social skills.

The parents have sought help relatively early in the course of the child's illness. Intensive behavioral and educational interventions will be necessary to help accelerate the child's development. The child will likely experience a number of developmental delays, but with intensive treatment at home and at school, he could achieve near-normal or normal development. Language development is the most important indicator of future developmental potential in ASD children.

ASD requires a well-rounded, multi-systemic treatment approach: family education, behavior shaping, speech therapy, occupational therapy, and educational planning. Care should be taken to coordinate these activities across school and home settings. Parental support and training are essential to a successful outcome. Applied behavioral analysis can be helpful in autistic patients, especially those with limited verbal skills. This treatment involves an intensive behavioral program that works best if started early in the course of the illness. The goals of this treatment are to teach the child a variety of basic skills, such as attending to adults, language use, and how to interact with peers, all of which can increase the child's ability to be more successful in educational as well as social settings.

No specific medications are used in treating the core symptoms of ASD, although some recent studies using low-dose risperidone show some promise. In addition, recent studies have shown that the use of aripiprazole may also be of benefit with the irritability symptoms of ASD.

The presence of ASD does not necessarily indicate intellectual disability (ID), but a large percentage (~40%) of autistic individuals also suffer from this disorder. ID is a classification of cognitive functioning involving both a low intelligence quotient (IQ) and impaired adaptive functioning. However, some ASD patients with ID demonstrate unusual or extremely precocious abilities, termed “islets of precocity”, such as the ability to perform extraordinary mathematical calculations although the child is cognitively impaired in other ways. An appropriate assessment of intellectual functioning in autistic patients is essential. Abnormalities of attention are common in patients with autism spectrum disorder, but an additional diagnosis of attention deficit hyperactivity disorder (ADHD) would only be given in those cases where attentional difficulties or hyperactivity exceeds that seen in those with comparable mental age. However ADHD, OCD, behavior disorders, and psychotic disorders can also be present in children with ASD. These conditions should be targeted and treated if the symptoms meet the diagnostic criteria for that particular illness. Proper recognition and treatment of comorbid psychiatric disorders can have a significant impact on the overall outcome for children with ASD.

Changes in the family dynamic. Children with ASD experience extreme anxiety when their usual routine is disrupted. In this case, Jimmy’s parents are about to be divorced and reside separately, which means that much of Jimmy’s usual routine and environment will be changed. In order to offset any anxiety and ensure a smooth transition to having his parents live in separate households, Jimmy’s parents should focus on instituting and maintaining a consistent behavioral program. It is also important to note that Jimmy’s parents are most likely under a great deal of stress with their impending divorce, and this could lead to discord within the family unit and additional disruption of Jimmy’s usual routines. A marriage and family therapist can assist in the resolution of family discord and provide support for Jimmy’s parents.

Case 2B: Emotion, limbic system

The amygdala, which is part of the limbic system, is the region affected in this patient. This case is adapted from a case study in the 5th edition of Purves (see Box 29D, pages 657-658) that describes a patient suffering from Urbach-Wiethe disease, which is an extremely rare autosomal recessive condition

that results in the bilateral calcification and atrophy of the anterior-medial temporal lobes, which is where the amygdala is located. We can surmise that the amygdala is affected based on the patient's symptoms and the function of the amygdala, which is described below. It is important to note that this case is not meant to involve an in-depth discussion of Urbach-Wiethe disease, but rather to introduce the students to the limbic system, using the amygdala as a starting point. Case 11 (Freddie Leeson) will also involve a discussion of the limbic system, with a focus on the limbic loop, which mediates reward and reinforcement.

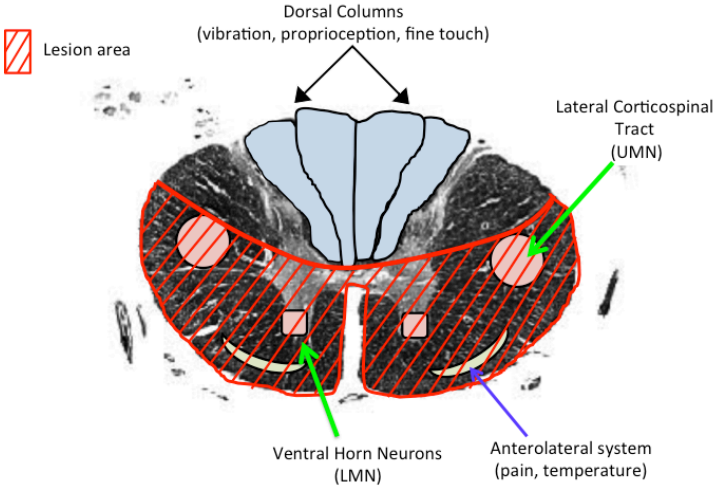
The amygdala is a gray matter nucleus buried deep in the anterior-medial region of the temporal lobe, just rostral to the hippocampus. The amygdala has extensive connections with cerebral/association cortex, hypothalamus and brainstem. The amygdala serves to link inputs about from cortical regions that process sensory information with effector motor systems (e.g., autonomic, enteric, somatic) in the hypothalamus and brainstem. Cortical inputs to the amygdala provide information about visual, auditory, somatosensory, visceral sensory, gustatory and olfactory stimuli. The projections from the amygdala to the hypothalamus and brainstem allows for the expression of emotional behaviors by influencing the activity of the somatic and visceral motor efferent systems. That is to say, the amygdala is involved in linking emotional significance with sensory experiences perceived by the association cortex, and in particular, can be involved in experiencing fear and the expression of fearful behaviors. For example, since the amygdala is a region where the neural activity produced by a number of modalities (e.g., visual, auditory) is processed, the amygdala can mediate fear conditioning, where the organism learns to associate an innocuous stimulus (e.g., a tone) with an aversive sensation (e.g., foot shock). The amygdala may also be involved in aggressive behavior, as non-human primates that have bilateral amygdalectomies (which constitutes Kluver-Bucy syndrome, a condition rarely seen in humans) are placid in situations that would normally induce fear or aggression (e.g., being in the presence of humans).

The limbic system consists of several individual components (including the amygdala) that form a complex network with multiple reciprocal connections. The limbic system is responsible for mediating olfactory, memory, emotional/motivational and homeostatic functions (including autonomic and neuroendocrine functions). The structures that comprise the limbic system extend from the forebrain to the brainstem and most of these structures lie deep within medial and ventral regions of the cerebral hemispheres. Other components of the limbic system include the limbic cortex, (consisting of the cingulate gyrus, medial orbitofrontal cortex and parahippocampal gyrus, and surrounding the corpus callosum), hypothalamus, septum, hippocampal formation and nucleus accumbens (which plays a role in reward as part of the limbic loop; see Case 11 for a more in-depth discussion). It is convenient (although somewhat simplistic) to assign individual limbic structures to each of these functions: olfactory cortex for olfaction, hippocampal formation for memory, amygdala (along with its complex interactions with other regions, such as limbic cortex and nucleus accumbens) for emotions/drives and hypothalamus for homeostasis. The amygdala has reciprocal connections with autonomic centers in the hypothalamus and brainstem, which underlies the physiological changes (e.g., sweating, changes in heart rate) that are commonly seen with strong emotions. Connections between the limbic cortex, amygdala and

hypothalamus are important for neuroendocrine changes that may be seen with different emotional states.

Cases 3C and 4C: Lesions in motor pathways, decerebrate/decorticate rigidity

Case 3C: The patient is suffering from an anterior spinal cord lesion (anterior cord syndrome) at the mid-thoracic level, which results in deficits in his lower extremities (see figure below).



Motor deficits: There are upper motor neuron (UMN) signs in both extremities due to interruption of both lateral corticospinal tracts at the thoracic level. These include weakness, hyperreflexia, hypertonia and positive Babinski's signs in both legs. There are lower motor neuron signs in the muscles of the trunk, due to a loss on inputs to the muscles that are innervated by lower motor neurons at the level of the spinal cord lesion.

Sensory deficits: The patient will have a loss of pain and temperature sensation in the lower extremities, due to bilateral interruption of ALS. The dorsal columns are unaffected by this lesion; therefore, fine touch, vibration and proprioception will remain intact.

Case 4C: This is a case of decerebrate rigidity, where all four limbs are extended with spasticity upon passive movement, most likely brought on by an undiagnosed/untreated epidural hematoma. When the patient hit her head during the accident, it is likely that the temporal bone severed the middle meningeal artery, leading to a relatively slow bleed in the temporal area that would have been asymptomatic after the initial head trauma. Over time and without intervention, the size of the bleed would have increased, resulting in increased intracranial pressure (ICP), herniation (perhaps central/transtentorial) and compression of the brainstem, leading to decerebrate rigidity (*note*: the patient most likely experienced decorticate rigidity before progressing to decerebrate rigidity-see explanation of decorticate rigidity below). With decerebrate rigidity, the level of the lesion (in our cause the compression caused by the bleed) is said to be between the peduncles, as decerebrate rigidity can be reproduced in the laboratory by transecting the brainstem between the superior and inferior peduncles. Decerebrate rigidity is considered an ominous sign, as it is indicative of the "lesion" moving more caudally down the brainstem, where centers for regulating respiration and heart rate are located in the medulla. Decerebrate rigidity is due to unopposed hyperactivity of the extensor muscles in all

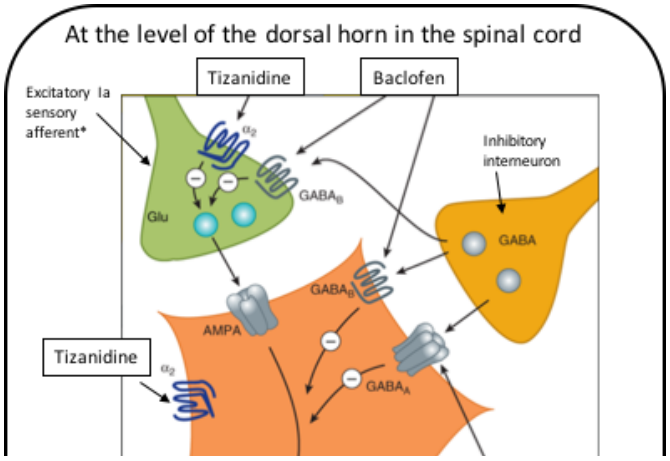
four extremities. The increased ICP/herniation will compress the crus cerebri (in the midbrain), and will interrupt the corticospinal tract. Remember that the corticospinal tract produces muscle contraction via direct activation of lower motor neurons, as well as through direct activation of gamma motor neurons (this has to do with the gamma motor loop-students will probably not know about this, but might ask), which through several steps leads to muscle contraction (or flexion). The end result is that loss of the descending corticospinal inputs leads to inactivity of the flexor muscles. The rubrospinal tract (which originates in the midbrain) is also interrupted in this scenario. In humans, the rubrospinal tract is thought mediate the activation of the limb flexors in the upper limbs; thus without an intact rubrospinal tract there is no flexor activity in the upper limbs. On the other hand, extensor motor neurons are unaffected by the loss descending corticospinal and corticorubral inputs because these motor neurons are activated by descending reticulospinal and vestibulospinal tracts that are not involved in the lesion; thus, the activity of these tracts remain intact, leading to extension of all four extremities.

As mentioned above, a patient may experience a period of decorticate rigidity before progressing to decerebrate rigidity. With decorticate rigidity, where the patient's upper limbs are flexed, while the lower limbs are extended, is due to a "lesion" that is just rostral to the superior colliculus (again, decorticate rigidity can be reproduced in the laboratory by transecting the brainstem just rostral to the superior colliculus). This lesion leaves the rubrospinal tract intact, which results in flexion of the upper limbs.

Case 3C: Because of the loss of corticospinal inputs to lower motor neurons, this patient will experience significant spasticity. Spasticity is due to dysregulation of the stretch reflex arc.

Remember that the stretch reflex arc involves inputs from Ia sensory neurons that carry information about the muscle (length, contraction) to the spinal cord, where they synapse on lower motor neurons that activate the muscle and induce a reflexive movement (Ia fibers may also synapse onto inhibitory interneurons in the spinal cord, which will inhibit lower motor neurons that innervate the antagonist muscle). Upper motor neurons modulate the activity of the stretch reflex arc. Typically, UMNs will inhibit the stretch reflex. If you remove the UMN input, then the stretch reflex arc will experience unopposed activation, leading to spasticity.

Drugs that modify the reflex arc may modulate excitatory or inhibitory synapses, leading to a reduction in spasticity. The reduction of the hyperactive stretch reflex can be accomplished via reducing the activity of the Ia sensory fibers that excite the lower motor neuron or via enhancement of the activity of the inhibitory interneurons in the spinal cord, which would inhibit the activity of the lower motor neuron.



Baclofen is a GABA-B receptor agonist. GABA-B receptors (which are inhibitory g-protein coupled receptors that reduce cAMP production and also open outwardly rectifying

K+ channels) are located on the cell bodies of lower motor neurons in the spinal cord, and their activation by baclofen will reduce the over-activity of LMNs that are involved in the unopposed activation of the stretch reflex arc, leading to decreased spasticity. GABA-B receptors are also located presynaptically on Ia afferents that provide sensory inputs to the spinal cord.

Benzodiazepines (e.g., diazepam) are GABA-A receptor agonists and may also be used to treat spasticity. GABA–A receptors are ionotropic receptors that located on the cell bodies of lower motor neurons. GABA-A receptor activation leads to an increase in Cl^- conductance through the GABA-A receptor, and hyperpolarization. Benzodiazepines are more sedating than baclofen, and are habit-forming.

Tizanidine is an alpha-2 adrenergic agonist. Alpha-2 adrenergic receptors are inhibitory G-protein coupled receptors, whose activation leads to decreased cAMP production and increased K+ conductance. These receptors are located on lower motor neuron cell bodies, as well as presynaptically on the excitatory (glutamatergic) inputs from Ia sensory inputs to the spinal cord or the corticospinal tract (if it's still intact).

Case 4C: A craniotomy should be performed immediately to drain the epidural bleed.

Case 5D: Association cortices, aphasias.

The patient in this case has most likely suffered a stroke that has affected his left hemisphere, resulting in damage to Broca's area and leading to Broca's aphasia. The cerebral hemispheres are specialized in terms of their function. The right hemisphere mediates spatial attention and emotion, while the left hemisphere mediates language. In roughly 95% of right handed individuals, and in about 70% of left-handed individuals, the left hemisphere is dominant for language. In general, a stroke in the right hemisphere (i.e. from a MCA infarct) will lead to left hemineglect with little or no obvious language disturbances, while a stroke involving the left hemisphere will result in language deficits or aphasias. The type and severity of the aphasia will depend on the specific regions of the left hemisphere that are impacted by the stroke. Two main regions for language processing and production are the association cortical regions designated as Broca's area, which is found in the inferior frontal gyrus of the dominant hemisphere and Wernicke's area, which occupies the posterior 2/3 of of the superior temporal gyrus of the dominant hemisphere. These structures are involved with linguistic processes, i.e., hearing a word and then repeating it. The initial step of language processing involves the identification of sequences of sounds to be identified and comprehended words. Auditory inputs to the primary auditory cortex reach the superior bank of the sylvian fissure in the temporal lobe, and the identification of sounds as words takes place in the adjacent Wernicke's area. The articulation of sounds that make speech are located in Broca's area, which includes the face area of primary motor cortex. The ability to hear a word and then respond aloud (with either repetition of the word that was heard or a response to the word that was heard) relies upon connections between Wernicke's and Broca's areas via the arcuate fasiculus. Neural representations of sounds are converted to words by Wernicke's area and neural representation for words are converted back to sound by Broca's area. Damage to either or both of these regions will result deficits in language processing.

Damage to Broca's area (i.e., stroke in the MCA superior division) results in impaired fluency of speech, which is usually manifested as shortened phrase length (<5 words/phrase), a lack of prosody (intonation) and impaired naming. Since lesions to Broca's area will cause a disconnection between Broca's and Wernicke's areas, there will be impaired repetition in those that suffer from Broca's aphasia. However, because the posterior language regions are spared in Broca's aphasia, comprehension remains normal. Reading aloud is impaired with Broca's as is writing, while reading comprehension remains intact. Those with Broca's aphasia are aware of their deficit, and may appear frustrated.

Damage to Wernicke's area (i.e., stroke in the MCA inferior division) results in impaired comprehension and speech that is fluent, but empty, meaningless and with nonsensical paraphrasic errors and occasional neologisms. Like Broca's aphasia, repetition is impaired with Wernicke's aphasia, as these regions will be disconnected by the lesion. Reading and writing also show impairments, in that comprehension is compromised, and writing will be fluent, but meaningless. Wernicke's aphasia may also be accompanied by contralateral visual field deficit (usually in the upper right quadrant, if the optic radiations through the temporal lobe have been affected by the lesion). Unlike Broca's aphasia, those with Wernicke's aphasia are unaware of their condition.

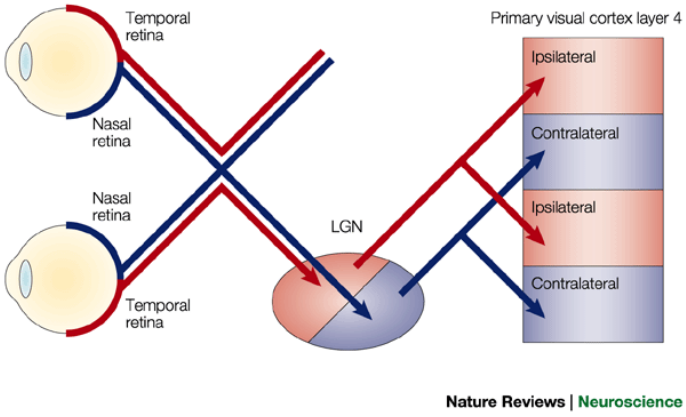
Global aphasia may also occur, if both Broca's and Wernicke's regions are affected (i.e., MCA stem infarct), where the patient is not fluent, unable to repeat words, and lacks comprehension. There are several other types of aphasia that may be observed such as transcortical aphasias, which resemble Broca's, Wernicke's or global aphasias, except that repetition is spared; these are usually caused by watershed infarcts that might spare the Broca's or Wernicke's but damage other language areas in the frontal or temporoparietal cortices.

Week 6

Case 6A: Neural plasticity and neurogenesis

The patient in this case is suffering from a misalignment of her eyes (strabismus). The goal of this case is not to prompt a discussion of the muscles that control the eye, but rather to introduce the concepts of neural plasticity and critical periods.

Several regions of the brain including visual cortex, have critical periods, where neural plasticity (or the ability for neurons to change their physiological responses/connectivity) is the most robust. Usually, these critical periods occur early in development during a specific developmental age, and as the organism ages, the ability to induce neural plastic changes diminishes. The plastic changes that occur during these critical periods are often activity dependent and rely upon inputs from the external environment. Hebb's postulate (coordinated activity of a presynaptic terminal and a post-synaptic neuron strengthens the synaptic connection them) was originally used to explain the cellular basis of learning and memory, but is also applicable in the context of critical periods, in that synapses that are strengthened by coordinated activity during development will be retained, while weakening of synapses can occur when there is uncorrelated activity.



The critical periods in visual system development have been studied extensively, and provide one of the best examples of neural plasticity and critical periods. Early studies in the field involved depriving visual input in one eye (by suturing the eye shut), and examination of the effects of the loss of input on the development of visual cortex. Normally, information from the two eyes is integrated in the visual cortex, and the afferent terminals from the lateral geniculate nucleus form ocular dominance columns, which are an alternating series of eye-specific regions in layer 4 of visual cortex (see figure below). This allows the animal to have binocular vision. The neurons in the cortex that make up the ocular dominance columns can be activated by either eye, as these columns contain inputs from both eyes. This normal distribution of the ocular dominance column can be altered by visual experience during the critical period. For example, if an eye is sutured shut early on in development, and the animal is matured to adulthood, once the eye is re-opened, there will be a resulting change in the responsiveness of the ocular dominance columns in the visual cortex, i.e., there will be a shift in the distribution of inputs to the ocular dominance columns. If the deprived (previously sutured) eye is stimulated, very few cortical cells in the ocular dominance column will be activated, whereas the stimulation of the eye that remained open can drive the activity of most of the cortical cells. Thus, the sutured eye has been functionally disconnected from the visual cortex, and as a result the animal will be behaviorally blind. This may be referred to as “cortical blindness” or amblyopia. Even if the formerly sutured eye remains open, there will be no recovery, if the critical period has passed. Conversely, suturing an eye shut after the critical period has passed will have no effect on the mature visual cortex.

In our case, the patient has a weak left eye, and cannot focus both of her eyes on the same point—that is to say, she does not have binocular vision. What this means is that there will not be binocular input to her visual cortex and as a result, the unaffected eye will be providing the majority of the visual input to the visual cortex. If her strabismus is not corrected before the end of the critical period for visual cortex development (the earlier the intervention the better; by ages 6-8, there seems to be less success in prevent/correcting changes to visual cortex) then her left eye will be functionally disconnected from the visual cortex. Placing an eye patch over the unaffected eye with forces the patient to use the affected eye, which will help strengthen her ocular muscles, so that both eyes can provide equal inputs to visual cortex, which will allow her to have binocular vision.

There are a number of neurotransmitters that modulate the cellular and molecular aspects of activity-dependent neural plasticity during the critical periods. Glutamate, acting through NMDA receptors, as well as GABA, working through local inhibitory connections, can mediate the cellular changes that take

place during critical periods. Brain-derived neurotrophic factor may also play via modulation of intracellular calcium.

Case 7B: Cerebrovascular disease, ischemic brain injury, CNIII involvement

The patient in this case suffers from the rupture of an aneurysm in the posterior communicating (PComm) artery arising from the internal carotid. Risk factors for an intracranial aneurysm include congenital anomalies in the cerebral vasculature, polycystic kidney disease, and atherosclerotic disease. Other common locations for berry aneurysms are the anterior communicating artery and the middle cerebral artery. A large unruptured aneurysm can result in symptoms that are due to mass effect or compression of nearby structures. A large unruptured aneurysm in the PComm can result in a painful cranial nerve III palsy, as CNIII travels just ventral to PComm after it exits the midbrain from between the cerebral peduncles. CNIII palsy presents as a droopy eyelid on the affected side (due to loss of innervation to the levator palpebrae), an eye that looks down and out on the affected side which will result in diplopia (loss of innervation of all extraocular muscles except for the superior rectus, which is innervated by CNIV, and the lateral rectus, which is innervated by CNVI), and a "blown pupil" on the affected side (due to a loss of innervation to the pupillary constrictor muscle).

Patients who experience the rupture on an aneurysm describe the event as "the worst headache of my life", followed by a rapid loss of consciousness. In the majority of aneurysm cases, a subarachnoid hemorrhage will occur as a result of the rupture of an aneurysm in the subarachnoid space. While a significant number of patients will die after the first rupture of an aneurysm, but patients who survive will often recover consciousness within minutes. Risk factors for the rupture of an aneurysm include hypertension, cigarette smoking, alcohol consumption, and situations that cause a sudden elevation in blood pressure.

Case 8C: Learning and memory, dementia and delirium

The patient in this case is suffering from dementia, which refers to a disease process that is marked by progressive cognitive, social and occupational impairment, without altered consciousness. Dementia is different from low intellectual functioning or mental retardation, as these are static developmental conditions, while dementia represents a decline from normal cognitive function. There are different types of dementia based on etiology: Alzheimer's disease (AD), dementia with Lewy bodies, vascular dementia, traumatic brain injury or other neurological/medical conditions (Pick's disease, Huntington's disease, Parkinson's disease, HIV, chronic alcoholism). One of the most common causes of dementia is Alzheimer's disease—this is the suspected cause of our patient's dementia, which is confirmed by the neuropathological findings on autopsy. The gross neuropathological findings in AD show diffuse neuronal atrophy, flattened sulci and enlarged ventricles (see Image 1 for this case). Microscopic findings typically include amyloid plaques, neurofibrillary tangles, and neuronal loss predominantly in the cortex and hippocampus.

Neurofibrillary tangles are composed of cytoskeletal elements, particularly phosphorylated tau protein, and most commonly found in the cortex and hippocampus. Neurofibrillary tangles are not unique to

AD-they may also be seen in other neurological disorders, such as chronic traumatic encephalopathy and Down's syndrome; they may also be seen in the brains of normal individuals as they age.

Amyloid plaques are focal, spherical collections of dilated neuritic processes around a central amyloid core (see Image 2 for this case-plaques are indicated by the arrows), and are also found primarily in cortical and hippocampal regions. These plaques are comprised of Aβ peptides, which are derived through processing the amyloid precursor protein (APP). APP is found on the cell surface, with the Aβ fragment extending into the extracellular region from the transmembrane region. APP processing begins with the cleavage (by proteolytic enzymes called secretases) of the extracellular region of Aβ, followed by cleavage of the transmembrane portion of Aβ. There are two possible pathways that are determined by the type of initial cleavage. If the first cleavage occurs at the α-secretase site on the extracellular region of Aβ, then Aβ is not generated—this is the non-amyloidgenic pathway. The amyloidgenic pathway occurs if the first cleavage is by β-secretase (also called BACE1), which cleaves at the N-terminus of the Aβ region. Following the cleavage of APP by either the α- or β-secretase, γ-secretase complex (which contains presenilin) will cleave APP at the transmembrane region. When the cleavage by γ-secretase is paired with a cleavage by α-secretase, a soluble fragment is formed, but then the cleavage by γ-secretase is paired by cleavage with β-secretase, soluble Aβ is formed, and readily aggregates resulting in synaptic dysfunction and the blockade of long-term potentiation (LTP), which is thought to be the cellular basis for learning and memory processes (see below). There are variations in Aβ length (Aβ40 or Aβ42) that are determined by the exact location of the γ-secretase cleavage. Neuritic plaques contain both Aβ40 and Aβ42, but Aβ42 is thought to be the most neurotoxic form of Aβ, and it is this form that is predominately seen in with AD. The gene for APP is located on the long arm of chromosome 21, and those who suffer from trisomy 21 (Down's syndrome) commonly suffer from early onset of AD.

The locus on chromosome 19 that encodes for apolipoprotein E (ApoE) can play a role in the development of AD. ApoE is thought to promote the generation of Aβ. Those that have the ε4 allele for the ApoE are at higher risk for developing AD. Indiviuals that have 1-2 copies of ε4 or 3-8 times more likely to develop AD than those who do not have the ε4 allele.

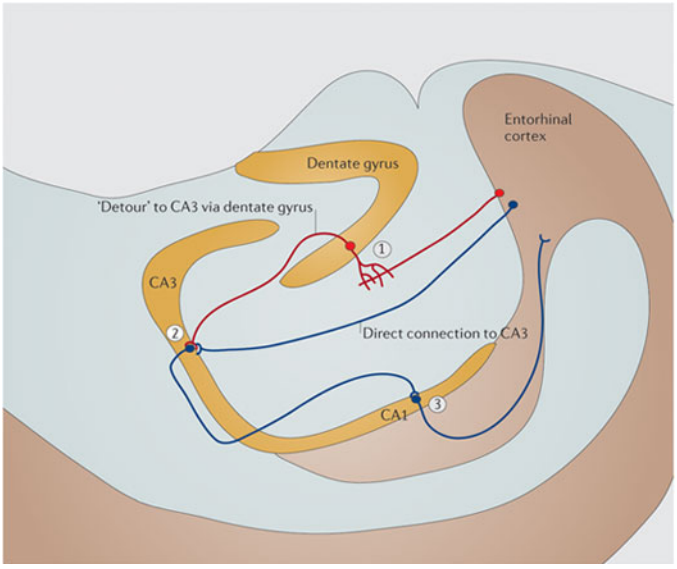
Hypoactivity of the acetylcholine (Ach) system is thought to contribute to the pathophysiology of AD, as the specific degeneration of cholinergic neurons in the basal nucleus of Meynert (BNM) is present in patients with AD. The cholinergic neurons of the BNM provide inputs to the cortex and hippocampus, and cholinergic inputs to theses regions are thought to be necessary for normal cognition and memory processes. The cholinergic inputs to the hippocampus are the first to be affected in AD, resulting in impairments in memory formation, with remote memory left relatively intact. However, as the disease progresses, cholinergic inputs to the cortex will be compromised, and this will result in deficits in remote memory, as the cortex is where long-term memories are stored.

Further support for impaired Ach neurotransmission in the pathophysiology of AD comes from the observation that antagonists at muscarinic Ach receptors (i.e., scopolamine, atropine) can impair cognition. Antagonists at muscarinic Ach receptors can also precipitate delirium. Delirium is

characterized by an acute decline in the level of consciousness and cognition, and an impairment of attention. Both dementia and delirium share the common symptom of cognitive decline, but delirium can be distinguished from dementia, based differences in clinical features. The onset of delirium is fairly rapid compared to dementia, with altered/decreased consciousness as a hallmark feature. Delirium also involves perceptual disturbances and abnormal psychomotor activity. Delirium can often be rapidly improved when the causative factor is identified and eliminated. There are multiple causes of delirium, such as CNS disease, intoxication, drug withdrawal (e.g., delirium tremens seen in chronic alcoholics), or toxin exposure. Ach neurotransmission in the reticular formation (a region in the brainstem that regulates attention and arousal) is thought to be involved in delirium. In our case, the patient takes an Ach muscarinic receptor antagonist (scopolamine) to ameliorate his motion sickness and experiences an episode of delirium that is resolved once the medication is discontinued. It is possible that because our patient may have already been experiencing a decline in Ach function, he may have been more sensitive to the anticholinergic effects of scopolamine.

Dementia associated with AD can be distinguished from other types of dementia based on clinical symptoms. For example, vascular dementia can be distinguished from AD based on the progression of the dementia. With AD, the progression of dementia is typically a gradual, but continuous decline while the progression of vascular dementia is often "step-wise" meaning the patient will experience plateaus (where the symptoms of dementia do not get any worse) in between periods of cognitive decline. Pick's disease is associated with atrophy of the frontotemporal region, and results in dementia that is qualitatively different from that seen with AD (at least in the early stages of Pick's disease; as Pick's disease progresses, it is difficult to distinguish between dementia caused by Pick's vs. dementia associated with AD). In the early stages of Pick's disease, dementia is often characterized by personality and behavioral changes (due to atrophy of the frontal cortex, which is responsible for the executive and emotional control of behavior) with a relative preservation of other cognitive functions. Lewy body disease presents with a dementia that is similar to that seen with AD, but is also accompanied by hallucinations and parksinonian features. Lewy bodies may be found in the cortex, as well as the substania nigra.

LTP is thought to be the cellular basis of learning and memory, and this process may be impaired in those who suffer from AD. LTP refers to the long-lasting strengthening of synapses, and is induced by synaptic activity at the pathway that is being potentiated. Explicit memory (which is the intentional and conscious recollection of facts, previous experiences and concepts), involves LTP in the hippocampus. Inputs to the hippocampus arise from the adjacent entorhinal cortex, which receives multimodal sensory and spatial information from other cortical regions (e.g., frontal, parieto-occipital and temporal association cortices)



Information from the entorhinal cortex enters the hippocampus as the perforant pathway, which ultimately form synaptic connections with the CA1 neurons in the hippocampus.

The perforant pathway sends excitatory inputs to CA3 neurons, which send excitatory projections to CA1 neurons via the Schaffer collaterals (some perforant pathway neurons may "detour" at the dentate gyrus before heading to CA3). LTP can occur at each of these synapses, but the type of LTP and the contribution of NMDA glutamate receptors can differ. The Schaffer collateral pathway that connects CA3 to CA1 is probably the best-characterized pathway, in terms of the mechanisms of LTP and the contribution to learning and memory processes. In this pathway, during normal synaptic transmission glutamate will be released from the CA3 neuron, which acts on NMDA and AMPA receptors on the post-synaptic CA1 neuron. Sodium and K^+ will flow through AMPA, but not NMDA receptors, as the amount of glutamate that has been released is not enough to significantly depolarize the CA1 neuron (the ion channel within the NMDA receptor is blocked by Mg^+ at negative membrane potentials; thus, the Mg+ block will remain during this low-frequency neurotransmission). With high-frequency neurotransmission, there will be a large depolarization of the post-synaptic CA1 neuron (due to strong activation of AMPA receptors), which will release the Mg^+ blockade from the NMDA receptor, which will allow the influx of Ca^{2+}, Na^+ and K^+ plus through the NMDA receptor. The entrance of Ca^{2+} postsynaptically triggers calcium dependent kinases, which will lead to the induction of LTP. The second messenger cascades activated during the induction of LTP will result in the insertion of additional AMPA receptors into the post-synaptic membrane, such that the post-synaptic CA1 neuron becomes more sensitive to subsequent glutamate neurotransmission (i.e., it now takes less glutamate to get depolarization). In addition, there will be production of retrograde messengers that can activate the presynaptic CA3 neuron to enhance subsequent neurotransmitter release. LTP has early and late phases. The early phase (which was just described) does not induce protein synthesis, and lasts 1-3 hours after stimulation. Late phase LTP (induced by several trains of stimulation) can last up to 24h and induces protein synthesis.

The CA1 neurons that participate in LTP are the major output neurons of the hippocampus and send projections back out through the entorhinal cortex. From the entorhinal cortex, outputs are sent to association cortices for the storage of long-term memories.

Acetylcholinesterase inhibitors that augment cholinergic neurotransmission are a common treatment for AD. These drugs include donepezil, rivastigmine and galantamine. Their side effects are similar to those seen with other AchE inhibitors that result in excess cholinergic stimulation: nausea, diarrhea, and vomiting. These drugs seem to produce a moderate improvement in cognitive function. Memantine, which is an NMDA receptor antagonist may also be used to treat AD, either as a monotherapy, or in combination with an AchE inhibitor. Memantine is non-competitive NMDA receptor antagonist, as memantine does not compete directly with Glu binding site. Memantine blocks NDMA receptors in a voltage-dependent manner. What this means is that that the ion channel must be open (i.e., the neuron must be depolarized) for drug to enter the channel. Memantine has relatively fast on and off rate at its binding site (i.e., it can bind to and dissociate quickly from the receptor).

While NMDA receptors are involved in LTP and memory formation, recent evidence suggests that sustained low levels of glutamate activity may underlie pathology of AD. Aβ peptide may also play a role, as it can increase the amount of glutamate released upon depolarization, bind directly to NMDA and decrease glutamate uptake by glial cells. This may lead to neuronal injury as excess glutamate can induce induce excitatoxicity, as a result of increased Ca^{2+} influx. Memantime blocks postsynpatic activity of moderately high levels of glutamate neurotransmission (in the μM range) that may be tonically active in AD. But memantine will allow activity caused by very high levels of extracellular glutamate (in the mM range) that occurs during LTP. Since memantine has a low affinity for the NMDA receptor, it's more likely to leave the channels when they're open, like during the high levels of glutamate binding that occur during LTP. Thus, memantine may be protective against NMDA receptor excitotoxicity, without interfering with LTP-mediated memory processes.

It is also important that the primary caregiver of the AD patient receives adequate support. Most often the primary caregiver is the patient's spouse or child, and the changes that occur in the patient can cause significant distress in the caregiver. Support groups and programs that are designed to provide caregivers with the necessary tools and information for caring for a loved one with AD are also an important part of treating the AD patient. In some cases, the caregiver may need to seek psychological counseling to learn how to deal with stress and the feelings of grief that may arise at the patient's dementia progresses.

Week 7

Case 9A: Eating disorders

The family physician's workup documents a very low BMI with some subtle findings of marked weight loss, but nothing indicative of an organ-specific disease. The laboratory findings are indicative of poor caloric intake, with low glucose (acute) and low albumin (chronic). The anemia is likely akin to anemia of chronic disease, but it may have elements of both iron deficiency and vitamin (B_{12} / folate) deficiency.

Features of anorexia nervosa may include:

- Dry skin
- Hypercarotenemia
- Lanugo body hair
- Acrocyanosis
- Atrophy of the breasts
- Swelling of the parotid and submandibular glands
- Peripheral edema
- Thinning hair

Characteristic signs of inadequate energy (caloric) intake observed in patients with anorexia nervosa

that are due to starvation-induced changes are summarized below. Positive signs include the following:

- Hypothermia
- Acrocyanosis
- Resting bradycardia (resting heart rate often 40-49 beats per minute)
- Hypotension
- Orthostatic lowered blood pressure or pulse
- Loss of muscle mass
- Low blood glucose (impaired insulin clearance)
- Low parathyroid hormone levels
- Elevated liver function tests
- Low white blood cell (WBC) count

Biopsychosocial aspects of the case. The 'bio' includes the physical manifestations of malnutrition and weight loss. The 'psychologic' is the patient's understanding / coping with the illness. She has appropriate functioning for activities of daily living and the mental capacity for employment. She does not recognize what is happening to her. The 'social' is the persons around her and her interactions. We have little information about her family's understanding of the illness or any intervention. No one else in the family is underweight, so inadequate nutrition is not a family issue. Labeling her family's appropriate concern as "nagging" supports that she does not recognize the health impacts of her significantly low weight.

Diagnosis. Ms. Gaspard's most appropriate DSM-5 diagnosis is anorexia nervosa (AN). Although her history suggests alternative explanations for her cachectic presentation, none is as compelling as AN. For example, avoidant/restrictive food intake disorder, newly named with revised criteria in DSM-5, could also present with an eating disturbance, significant malnutrition, and either a lack of interest in or an aversion to eating triggered by or associated with a range of physical complaints, including gastrointestinal discomfort. However, Ms. Gaspard's bloating and nausea are a red herring: both are common in AN, where they can be idiopathic or associated with delayed gastric emptying or whole-gut transit time. Similarly, although major depressive disorder can also be associated with appetite loss, Ms. Gaspard is euthymic and actively engaged in her missionary work. Lastly, although Ms. Gaspard's limited access to food and transportation may contribute to her malnutrition and excessive physical activity, it is notable that no one else in her family (with whom she shares communal resources) is underweight.

Because Ms. Gaspard does not engage in binge eating (i.e., she denies eating large amounts of food while feeling out of control) or purging (i.e., she denies self-induced vomiting or abuse of enemas, laxatives, diuretics, or other medications), her presentation is consistent with the restricting subtype of AN. An elevated risk for an eating disorder following immigration from a culturally non-Western to a Western country has been described for some populations, attributed to increased exposure to Western beauty ideals as well as stressors associated with acculturation.

Although Ms. Gaspard would not have met DSM-IV criteria for AN because of her lack of fat phobia and

her continued (albeit irregular) menses, she meets revised DSM-5 criteria for AN. The first criterion for AN is significantly low weight. Ms. Gaspard's BMI of 14.7 places her below the first BMI centile for U.S. females of her age and height. Furthermore, her BMI is well below the World Health Organization's lower limit of 18.5 kg/m^2 for adults. Her weight is so low that her menses have become irregular. It is important to note that amenorrhea (i.e., lack of menses for 3 months or more) is a DSM-IV criterion for AN but is omitted from DSM-5 due to research suggesting that low-weight eating-disorder patients who menstruate regularly exhibit psychopathology commensurate with that of their counterparts with amenorrhea. A second criterion for AN is either an intense fear of fatness or persistent behavior that interferes with weight gain despite a significantly low weight. Ms. Gaspard's rationales for food refusal are inconsistent with the intense fear of weight gain that DSM-IV previously characterized as the sine qua non of AN. However, many low-weight patients—especially those from culturally non-Western backgrounds—do not explicitly endorse weight and shape concerns.

Culture-based differences—including prevailing local norms that govern many factors, including dietary and meal patterns, aesthetic ideals for body shape and weight, embodiment of core cultural symbols and social relations, self-agency and self-presentation, and somatic idioms of distress—potentially influence the experience, manifestation, and articulation of eating pathology. For example, a clinical narrative that links restrictive eating behaviors to weight management goals can be easily formulated for a patient whose social context associates prestige with thinness, stigmatizes obesity, and assigns high value to achievement and autonomy.

The determinative cultural underpinnings of conventional AN presentation are perhaps best illustrated in Sing Lee's work from Hong Kong documenting "non-fat-phobic anorexia nervosa," a variant of eating disorder that strongly resembles DSM-IV AN except for its absent fear of weight gain. Lee and colleagues argued that fear of fatness had insufficient cultural salience for many of their patients, who rationalized extreme dietary restriction differently but nonetheless reached a dangerously low weight. Evidence that the absence of fat phobia may be associated with a more benign clinical course raises compelling questions about not just cultural mediation, but also cultural moderation of eating pathology. Globalized commerce and communication have opened avenues for broad exposure to what Sing Lee termed a "culture of modernity," and eating disorders are now recognized as having wide geographical distribution. The amendment in DSM-5 of AN Criterion B now encompasses individuals like Ms. Gaspard who exhibit persistent behavior that interferes with weight gain, even if they do not explicitly endorse fat phobia. Indeed, Ms. Gaspard's low food intake (600 calories per day) and high level of physical activity (3–4 hours per day) are clearly at odds with her stated desire to gain weight, however earnest her pronouncements may sound. Moreover, her myriad rationales for her restricted dietary intake (ranging from lack of hunger to forgetfulness to lack of resources) slightly undermine the credibility of each individual one. Following Ms. Gaspard over time to ascertain that her behaviors are persistent would help confirm the AN diagnosis, but her clinical history suggests that when Ms. Gaspard has previously been confronted about her low weight (i.e., by her family, by the dietitian), she has been either unwilling or unable to implement changes that would restore her to a healthy weight.

A diagnosis of AN also requires that a third criterion be met: a disturbance in the experience of one's body or shape, undue influence of that weight or shape on self-evaluation, and/or a lack of recognition of the seriousness of low weight. Ms. Gaspard denies an altered self-image and says she is worried about her low weight. However, her lack of follow-through with an earlier dietary intervention and her subsequent presentation to primary care to manage the symptoms of her dehydration and malnutrition (i.e., headaches, fatigue, poor concentration) suggest that she may not grasp the seriousness of her low weight. Furthermore, Ms. Gaspard's characterization of her family's appropriate concern as "nagging" supports that she does not recognize the health impacts of her significantly low weight.

Anorexia nervosa is difficult to treat because of the shame, denial, and lack of insight concomitant with the disorder. Medical management is directed toward correcting and preventing the disease's complications. Reestablishing normal eating patterns is crucial to restoring the patient's health. Hospital admission may be indicated for patients who are extremely ill, have cardiac dysrhythmias, or have severe metabolic abnormalities. Most patients will be admitted to medical facilities for refeeding, referred to psychiatric facilities and counseling if medically stable, or be managed on an outpatient basis.

Outpatient treatment should be undertaken only with very close monitoring, such as weekly weight measurement with the patient wearing only a gown. As with all psychiatric and behavioral emergencies, care must be taken to prove and document competency upon discharge. Many patients with anorexia nervosa may have additional psychopathology, which may leave them incapacitated during an anorexic crisis. If doubt remains, the patient must be admitted for more thorough psychiatric and physiologic monitoring or be discharged in the care of a competent caretaker. Transfer to an inpatient psychiatric facility may be the disposition for patients who are medically safe for discharge but who require aggressive inpatient psychiatric treatment of their disorder.

Acute pharmacologic treatment of anorexia nervosa is rarely required. However, vitamin supplementation with calcium should be started in patients, and although estrogen has no established effect on bone density in patients with anorexia nervosa, estrogen replacement (i.e., oral contraceptives) has been recommended for the treatment of osteopenia; the benefits and minimal effective dose of the hormone are being explored.

See also: http://emedicine.medscape.com/article/912187-treatment#showall

Differential diagnosis: physical exam findings shown in image 4. The oral cavity findings include mucosal ulceration and dental caries – features suggesting bulimia, in which purging would expose the mouth to gastric acid. The condition characterized by binge and purge eating is another eating disorder known as bulimia. There may also be a history of laxative and diuretic use. Such persons often have a history of substance abuse. This disorder is also dangerous, because the sufferer is typically concerned about body image and tends to be underweight and malnourished. Anxiety and depression often underlie bulimia, and these persons can be impulsive, with little concern for the consequences of their actions. Bulimic persons may have sialadenosis, or painless salivary gland enlargement.

Case 10B: Cerebellum

This is a case involving a space-occupying lesion (pilocytic astrocytoma) in the posterior fossa of a child.

The headaches are probably due to elevated CSF pressure from obstructive occlusion of the 4th ventricle. Headaches are worse during periods of highest CSF pressures (coughing, sneezing and bending down). The presence of bilateral papilledema is also indicative of an increase in intracerebral pressure.

The tumor (or displacement of the brainstem) appears to be impinging upon the right trochlear nerve (after it has crossed the midline on the dorsal surface of the midbrain), and this has led to a paresis of the left superior oblique muscle controlling eye movement. The trochlear nerve palsy produces weakness of downward eye movement with consequent vertical diplopia because the affected eye drifts upward relative to the normal eye, due to unopposed actions of remaining intact extraocular muscles. To compensate, the patient tilts the head forward in order to bring the visual fields back together.

The cerebellum mediates the smooth coordination of ongoing movements, and does not have direct connections to lower motor neurons. Rather, the cerebellum (much like the basal ganglia) exerts its effects through its connections to motor systems in the cortex and brainstem. The cerebellum is divided into functional regions that modulate different aspects of coordinated movement. The inferior vermis and flocculonodular lobes (which lie on the midline of the cerebellum) regulate balance and eye movements via interactions with vestibular nuclei, with the intermediate region (lateral to the vermis) modulating motor systems involving distal appendicular muscles, and the lateral cerebellar hemispheres mediating motor planning. Lesions of the cerebellum result in uncoordinated movement or ataxia. The ataxia observed with a cerebellar lesion is always ispilateral to the lesion (unlike lesions involving the cortex or basal ganglia), which is due to the "double-crossed" nature of cerebellar input-output pathways. Lesions to the vermis, along the midline of the cerebellum will result in truncal ataxia and eye movement abnormalities (often accompanied by nausea, vomiting), while lesions lateral to the vermis will result in ataxia of the limbs, which can been seen in the finger to nose test, where the patient is unable to direct the finger in a smooth and coordinated manner along with overshooting and overcorrecting of the movement (dysmetria). Dysdiododyskinesia (an inability to perform rapid, alternating movements) will also be present. Patients may also present with a wide based gait, which is an indication of truncal ataxia.

The patient is given a Romberg test in order to examine DC-ML integrity, as damage to the DC-ML can also result in issues with balance. A patient with a DC-ML lesion will have considerable more difficulty standing without swaying with eyes closed rather than open. A person with a cerebellar lesion will have roughly equal difficulty standing with feet close together without swaying, eyes open or closed. In this case, the fact that the patient did not sway more with eyes closed suggests the DC-ML system is intact.

Case 11C: Neurodegenerative diseases affecting the motor system, basal ganglia

The basal ganglia, along with the cerebral cortex (which give rise to upper motor neurons; UMNs), and several other structures (e.g., thalamus, cerebellum) work together to produce controlled voluntary

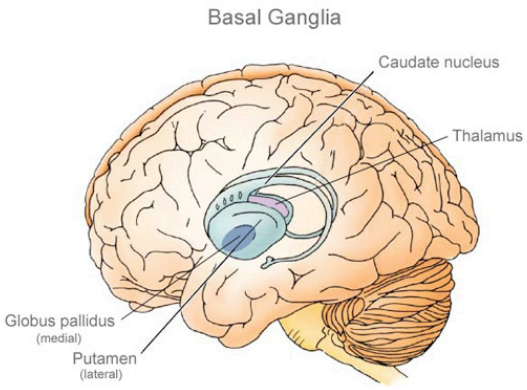
movement. The basal ganglia do not have direct access to lower motor neurons. Rather, the basal ganglia control movement via regulation of upper motor neurons. Inputs about the environment are received from the cortex, and the basal ganglia will suppress unwanted movements while preparing UMNs for the initiation of the appropriate movement. This circuit forms a sort of a loop, where the information originates in the cortex, is filtered through the basal ganglia where the correct motor program is selected and then routed back to the cortex, via the thalamus for the execution of the movement. Basically, this is a subcortical loop that connects almost every region of cerebral cortex with UMNs in the motor/premotor cortices and brainstem. There are different loops for processing different types of information and the execution of specific behaviors. For example, there is a motor loop, which mediates movement, and a limbic loop that deals with emotional behaviors. In short, the basal ganglia integrate and modulate cortical information along multiple parallel channels; these channels affect behavior by providing inputs back to the cerebral cortex and by providing information to subcortical centers that influence movement.

In order to understand how the basal ganglia function, it is important to keep the following concepts in mind:

1.) Damage or disorders of the basal ganglia result in a disruption of movement
2.) The basal ganglia are segregated into parallel circuits that process different types of behaviorally significant information
3.) The basal ganglia function primarily through *disinhibition*
4.) Diseases of the basal ganglia can be described as disruptions in the neurochemical elements of the basal ganglia (i.e., neurotransmitters, receptors, synapses)

There are four main components of the basal ganglia:

- Caudate and Putamen (striatum)
- Globus pallidus (internal and external segments)
- Subthalamic Nucleus
- Substantia Nigra (pars compacta, pars reticulata)



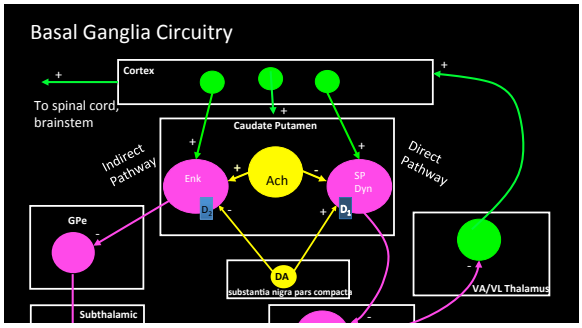
The caudate and putamen are the main input nuclei of the basal ganglia, while the globus pallidus internal segment/substantia nigra pars reticulata are the major output nuclei of the basal ganglia.

Motor nuclei of the basal ganglia are the caudate and putamen (striatum), which are also the major input nuclei of the basal ganglia. These nuclei are comprised of medium spiny neurons (MSNs), which are the target of all the axons arriving form the cortex. These MSNs have large dendritic trees, which allow them to integrate a large variety of inputs from cortex (and also thalamus and BS). Glutamatergic axons form synapses on the spines of the dendrites of MSN, with a single MSN receiving inputs from many corticostriatal axons. In other words, there is a large amount of divergence in the striatum, which allows a single MSN to integrate information from many, many cortical neurons. Almost all regions of cortex project to the striatum, with the densest projections arising from association cortices in the parietal and frontal lobes (association cortices don't process just one type of sensory information, but receive and integrate input from other sensory cortices). There are also functional differences in the inputs to caudate and putamen. The caudate receives inputs from multimodal association cortices and from motor areas in the frontal lobes that control eye movement. The putamen receives inputs from primary and secondary sensory cortices, motor/premotor cortices, and higher order visual and auditory cortices. This arrangement suggests that there are different parallel loops in place to process different types of information. The striatum also receives a dense dopaminergic projection from the substantia nigra pars compacta located in the midbrain.

The MSNs of the striatum exhibit very little spontaneous activity and must simultaneously receive excitatory input from the cortex and SNpc in order to fire an action potential (these neurons have inwardly rectifying K^+ channels that are open at resting membrane potential, but close with depolarization). When the MSNs do fire, it is associated with the occurrence of a movement, with a great deal of firing taking place in anticipation of the movement. This suggests that there is a movement selection process, as this burst of firing can occur several seconds before the initiation of the movement.

MSNs then send inhibitory projections to the globus pallidus (GP) and substantia nigra pars reticulata (SNpr; together they are the pallidal complex). These neurons in the GP/SNpr give rise to the major output pathways that allow the basal ganglia to influence the activity of UMNs in the motor cortex and brainstem. This path to the cortex arises from the GP internal segment (GPi), and sends an inhibitory projection the VA/VL nuclei of the thalamus. These thalamic neurons then project directly to cortex, thereby completing the loop. The SNpr synapses on the neurons of the superior, which mediate head and eye movements-this is done without a thalamic relay.

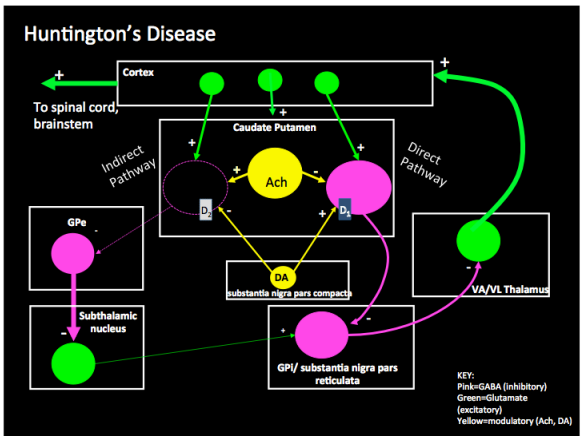
As mentioned, the projections from the Gpi/SNpr are GABAergic, so the main output of the basal ganglia is inhibitory. Unlike the MSNs of the striatum, the neurons of the pallidal complex are tonically active to prevent unwanted movement via inhibition of the thalamus. So in the absence of voluntary movement, the GPi/SNpr neurons tonically inhibit the thalamus. Keep in mind that the inputs to the basal ganglia--through the striatum-are excitatory, and the neurons of the striatum are inhibitory. So the net effect of excitation of the striatum by the cortex is to inhibit the tonically active inhibitory neurons of the Gpi/SNpr, which would result in disinhibition of the thalamus and excitation of the UMNs in the cortex. For voluntary movement to occur, there must be



inhibition of the Gpi/SNpr, and disinhibition of the thalamus.

Voluntary movement is mediated by the relative activity of two pathways that arise from the striatum: the direct and indirect pathways. Direct pathway neurons express excitatory D1 dopamine receptors, and send inhibitory projections directly to the GPi/SNpr; indirect pathway neurons express inhibitory D2 dopamine receptors, and send inhibitory projections to the GPe, which then projects to the subthalamic nucleus, and on to the GPi/SNpr. Both pathways receive dopaminergic inputs from the substantia nigra pars compacta (SNpc) in the midbrain. Excitation of the direct pathway facilitates movement, while excitation of indirect pathway suppresses movement. Thus, for voluntary movement to occur, the direct pathway must be activated and the indirect pathway suppressed.

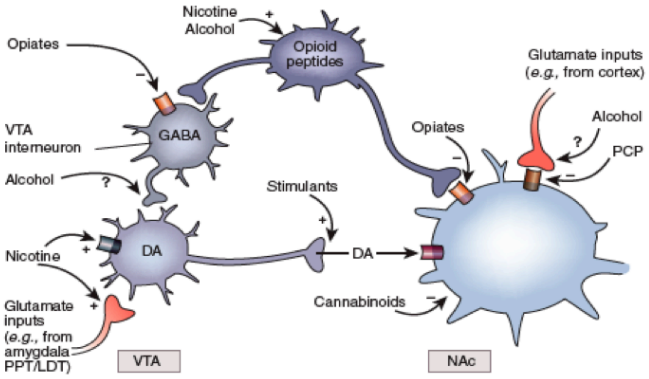
Activity in the cortex activates both direct and indirect pathways. Activation of the direct pathway neurons will inhibit pallidothalamic neurons. At the same time, activation of the indirect pathway neurons inhibits pallidosubthalamic neurons, which disinhibits subthalamic neurons, which excites pallidothalamic neurons. But for appropriate voluntary movement to occur, there must be modulation of the circuit by DA. As mentioned earlier, the MSNs of the striatum exhibit very little spontaneous activity. For direct pathway neurons to be fully activated and facilitate movement, they must simultaneously receive excitatory input from the cortex and SNpc in order to fire an action potential. At the same time DA will inhibit the activity of the indirect pathway neurons in the circuit to release the desired movement from inhibition.



With Huntington's disease (HD), there is a disproportionate loss of the neurons of the indirect pathway, which increases excitatory drive to the cortex, producing involuntary choreiform movements. End stage HD is characterized by a loss of both direct and indirect pathway neurons, and a complete loss of voluntary movement. HD is also associated with cognitive dysfunction, most likely due to the disruption of the basal ganglia loops through the caudate nucleus that mediate cognition; limbic loops through the basal ganglia may also be affected, leading to emotional changes. HD is an autosomal dominant disorder with almost complete penetrance, with an average age of onset between 35 and 45 years of age. HD is associated with a polymorphic CAG trinucleotide repeat on chromosome 4that is expanded in those who suffer from the disease (normal CAG repeat length=9-34 triplets; CAG repeat length in HD=40-100 triplets). Treatment for HD is often symptomatic. Depression associated with HD can be treated with antidepressants, while benzodiazepines can be used to treat anxiety (which an exacerbate involuntary movement) and low

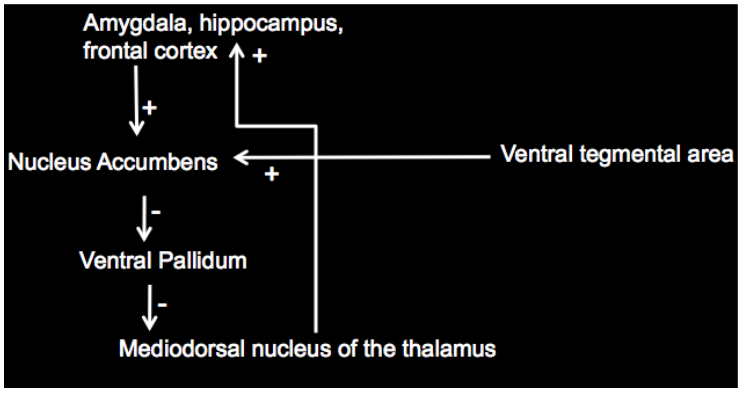
doses of antipsychotics can be used treat psychosis/delusions. Compounds that can impair cognitive function (e.g., anticholinergic compounds) should be avoided. Treatments for HD itself are limited to tetrabenazine or reserpine, which deplete presynaptic catecholamines via inhibition of the vesicular monoamine transporter-2 (VMAT-2; this prevents vesicular packaging of dopamine, thereby reducing the amount of dopamine released by the presynaptic neuron). These compounds can also cause depression with suicidality.

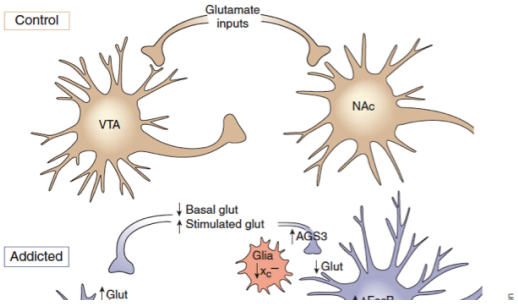
Case 12A: Drugs of abuse, limbic system



All drugs of abuse, regardless of their individual mechanisms of action, result in increased dopamine release in the mesolimbic pathway—this is the pathway that connects the ventral tegmental area with the nucleus accumbens, and forms part of the basal ganglia limbic loop that is important for emotion, as well as reward and reinforcement. With repeated exposure to drugs of abuse, dependence and addiction may develop, although the neural mechanisms that underlie the switch from abuse to addiction are not completely understood.

The limbic loop (see diagram below) is a pathway for the activation of non-motor (e.g., cognitive, emotional) programs. The release of dopamine in the nucleus accumbens encodes for the prediction of reward. Normally sensory cues that are first produced by and then associated with natural reinforcers (food, sex) activate reward pathway (increase DA release in Nac), which teaches the organism about evolutionarily useful behaviors (i.e., behaviors that keep the species alive). Drugs of abuse directly activate this circuitry via chemical means, bypassing the need for learning about evolutionary useful behaviors. In other words drugs of abuse can override the prediction signal and cause an unusually strong and inappropriate learning signal and the brain can't distinguish between the two. Basically, any activity that activates this circuit, whether it is related to survival of the species or drug-taking, is regarded as a behavior that should be repeated.





Adaptations to this system can occur with repeated drug exposure. Over time, with repeated drug use,

there will be an impairment of the dopamine system, which may contribute to tolerance to the effects of the drug and also dysphoria during withdrawal (dysphoria=depressed mood, and is thought to be modulated, in part by dopamine neurotransmission in the mesolimbic system). Since there are decreased basal levels of dopamine and glutamate, normally rewarding stimuli may be less effective in producing the same increases in dopamine transmission. At the same time, the dopamine system becomes sensitized to the drug(s) in question, as you see enhanced DA release with the exposure to the drug itself or drug-associated cues. The sensitization of the dopamine response to exposure to drug-related cues, along with long-lasting morphological and protein expression changes in the neurons of the nucleus accumbens may contribute to drug craving, as these effects last long after the drug is gone; these neuronal changes may also contribute to the relapse into drug-seeking behaviors.

Opiates (e.g., heroin, oxycodone, hydromorphone, fentanyl) produce their euphoric and sedative effects through activation of mu opioid receptors; they also increase dopamine release in the mesoaccumbal pathway through disinhibition of GABAergic neurons in the ventral tegmental area. With opiate overdose, there is increased activation of mu opioid receptors in the brainstem, leading to a decrease in heart rate and respiration, which could lead to death. Opiate overdose can be reversed with naloxone, which blocks mu opioid receptors.

Opiate withdrawal is characterized by a syndrome that includes nausea, vomiting, sweating, tachycardia, and hypertension. This is due to loss of opiate inhibition of locus coeruleus during abstinence. Opiates inhibit activity in the LC and once the opiates are removed there is a rebound effect such that there is now enhanced activation of the locus coeruleus, which results in nausea and vomiting. Initial detox may include treatment with clonidine, which is an alpha-2 adrenergic receptor agonist alleviates the symptoms withdrawal by decreasing norepinephrine release from locus coeruleus. Initial detoxification may depend on cross-tolerance to reduce the signs and symptoms of withdrawal, by taking advantage of the tolerance that has developed from whatever opiate the patient is addicted to so that you can change the short acting opiate that they've been abusing for a long acting opiate like methadone. Eventually the patient can be weaned off methadone with a less severe withdrawal syndrome.

Long-term management of opiate addiction may involve the use of methadone or buprenorphine. Methadone has a long duration of action, binds with high affinity to the mu opioid receptor, but is less psychotropic than commonly abused opiates (although it is not completely without psychotropic effects). Patients receiving methadone will not experience the ups and downs between being high and sick (as the abused opiate wears off) that they may have experienced while on the opiate that they have been abusing. It is thought that this lack of fluctuation will reduce drug craving and drug seeking-behaviors. Because of cross-tolerance (from methadone to the abused opiate), patients who inject street heroin report a reduced effect from usual heroin doses. However, methadone still has potential for abuse, and can cause overdose and must be given in a highly controlled methadone program. Buprenorphine binds to mu opioid receptors with high affinity (like methadone), but is a partial agonist meaning that it does not fully activate mu opioid receptors. Buprenorphine may be a safer alternative to methadone, as there is a lower risk for respiratory depression and overdose. Buprenorphine also has a milder withdrawal syndrome, doesn't require a traditional opioid treatment program and can be administered at an office practice. Buprenorphine is available in an oral formulation as subutex

(buprenorphine alone) or as suboxone (buprenorphine plus naloxone). Subutex may be abused, but pharmacological measures have been taken with suboxone to try in circumvent it's abuse. Naloxone is not orally active, so patients taking suboxone will still experience the benefits withdrawal treatment. However, if the patient tries to inject suboxone, the naloxone will then be pharmacologically active and will precipitate withdrawal.

Nicotine (obviously) acts on nicotinic Ach receptors, and can increase dopamine release in the mesoaccumbal pathway via direct stimulation of nicotinic receptors on the dopamine neurons of the ventral tegmental area. Varenicline, which is a partial agonist that binds with affinity to nictonic receptors (which means that it will act as an antagonist in the presence of a full agonist, such as nicotine), is commonly used for the pharmacological management of nicotine addiction. The FDA has published warnings associated with varenicline. Patients on varenicline may experience neuropsychiatric symptoms or exacerbation of pre-existing psychiatric conditions; agitation, hostility, depression, suicidal ideation and behavior have been observed.

Alcohol has a rather messy mechanism of action; it acts on GABAergic receptors to induce sedation, but may also act on other receptors, such as NMDA receptors. While it has been shown that alcohol increases the release of dopamine in the mesoaccumbal pathway, the exact mechanism is not completely understood. Withdrawal from chronic alcohol abuse includes nausea, vomiting, sweating, tachycardia and seizures (all due to massive rebound activation of neural systems after the removal of alcohol-induced inhibition). Alcohol withdrawal can potentially be lethal. Short-term detoxification may involve the use of a benzodiazepine to ameliorate the symptoms of withdrawal, although longer-acting benzodizapines should be avoided if liver function is compromised, as they are metabolized by the liver. For long term management of alcohol addiction, pharmacological approaches may be used, although no one drug seems to be particularly effective in preventing relapse.

Disulfiram is an aldehyde dehydrogenase inhibitor. Alcohol results in the production of acetylaldehyde, which is broken down to carboxylic acid by aldehyde dehydrogenase. Normally acetylaldehyde does not accumulate in the blood. When taken alone, disulfiram is benign but if it is taken with alcohol, acetylaldehyde levels in the blood increase (because acetylaldehyde can't be broken down by aldehyde dehydrogenase) leading to vasodialation, copious vomiting, respiratory difficulties and hypotension. Because of these side effects, disulfiram therapy must be done under careful medical supervision. Patients must be sure to avoid anything that might contain alcohol and should be given 12h after last drink. Naltrexone may also be used for long-term management of alcohol abuse. Naltrexone is a long-acting mu opioid receptor antagonist, and it is thought to block alcohol-induced activation of dopamine pathway, thereby reducing the urge to drink. Acamprosate is a GABA analog, and has been shown to reduce drinking frequency.

Addiction is thought to have a genetic component and an individual who has a primary relative that suffers from addiction is more likely to suffer from the same affliction.

In addition to pharmacological therapy, behavioral/psychological therapy is also important for the treatment of addiction. The combination of pharmacological and psychological therapy is more effective their either alone.

Case 13B: Personality Disorders

The patient in this case suffers from borderline personality disorder. Personality disorders are relatively common and chronic, are often co-morbid with other clinical syndromes, and are a predisposing factor for other psychiatric disorders. Individuals with personality disorders are less likely to seek psychiatric help and may deny that they have a problem, unlike other psychiatric disorders, such as anxiety or depression. Those with a personality disorder have little insight into their condition and typically do not experience anxiety about their maladaptive behaviors. These factors make personality disorders especially difficult to treat.

Personality disorders can be divided into three different clusters, based on their features: cluster A (schizotypal, schizoid, paranoid), cluster B (narcissistic, borderline, antisocial, histrionic), cluster C (obsessive-compulsive, dependent and avoidant). Cluster A personality disorders share odd and aloof features, while cluster B personality disorders share dramatic, impulsive and erratic features and cluster C personality disorders share anxious and fearful features. Personality disorders most likely have a genetic component, although the specific gene(s) involved in these disorders have not been identified. However, certain personality disorders are more common in biological relatives of patients with specific psychiatric disorders. Cluster A personality disorders are more common in the biological relatives of patients with schizophrenia, while depression is commonly seen in the family backgrounds of those with cluster B personality disorders. Anxiety disorders are often associated with cluster C personality disorders. It is also not unusual for an individual to suffer from more than one personality disorder.

Individuals with borderline personality disorder characterized by an extremely unstable affect, mood, self-image and object relations. These experiences often result in impulsive actions and unstable relationships. A person with BPD may experience intense episodes of anger, depression, and anxiety that may last from only a few hours to days. Some people with BPD also have high rates of co-occurring mental disorders, such as mood disorders, anxiety disorders, and eating disorders, along with substance abuse, self-harm, suicidal thinking and behaviors, and suicide. People with BPD may experience extreme mood swings and can display uncertainty about who they are. As a result, their interests and values can change rapidly. Other symptoms of borderline personality disorder include frantic efforts to avoid real or imagined abandonment, a pattern of intense and unstable relationships with family, friends, and loved ones, often swinging from extreme closeness and love (idealization) to extreme dislike or anger (devaluation), a distorted and unstable self-image or sense of self, impulsive and often dangerous behaviors (i.e., spending sprees, unsafe sex, substance abuse, reckless driving, and binge eating) and recurring suicidal behaviors or threats or self-harming behavior, such as cutting. A person suffering from borderline personality disorder may also exhibit intense and highly changeable moods, with each episode lasting from a few hours to a few days, chronic feelings of emptiness, inappropriate, intense anger or problems controlling anger, having stress-related paranoid thoughts, having severe dissociative symptoms, such as feeling cut off from oneself, observing oneself from outside the body, or losing touch with reality. Seemingly ordinary events may trigger symptoms. For example, people with BPD may feel angry and distressed over minor separations—such as vacations, business trips, or sudden changes of plans—from people to whom they feel close.

Borderline personality disorder (and personality disorders in general) is difficult to treat, and often

involves a combination of psycho- and pharmacotherapy. Psychotherapy is typically difficult for both the therapist and the patient, as patients can easily regress, act out their impulses and are emotionally labile, which is difficult for the therapist to analyze. Behavioral therapies may be used to control the patient's impulsivity and to reduce sensitivity. Pharmacotherapies include antipsychotics to lessen hostility and reduce brief psychotic episodes, while benzodiazepines can reduce anxiety (although some patients may show disinhibition with these compounds). Selective serotonin reuptake inhibitors and monoamine oxidative inhibitors may also be helpful for some patients.

Case 14C: Student abuse and impairment

Student impairment may be the result of a number of factors such as stress, anxiety, depression and substance abuse. At MUSM, student impairment is defined as behavior that violates the regulations of the school, or the accepted standards of the medical profession. It is recognized that the student's behavior may be the result of an inability to handle the stress of medical school, drug abuse/dependence or a psychiatric disorder. Often the factors that contribute to student impairment co-exist, and may one factor exacerbate the other (e.g., increased anxiety may contribute to increased substance abuse). Stress is often cited as the most common cause of impairment amongst medical students. Stress in and of itself may impair functioning, but may also lead to a number of other issues that can also contribute to the impairment of a student, such as depression, anxiety or substance abuse. Impairment may manifest as changes in behavior, emotional exhaustion, decreased performance, irritability or intoxication during school/work. It is important that impairment is recognized and addressed, as it can result in significant educational issues for the student (e.g., dismissal from medical school due to poor grades), or eventually potential errors in patient care. Medical students, as well as physicians have a professional duty to recognize impairment, either in themselves or in their colleagues, in order to protect the individual, patients, and the profession of medicine. There are several approaches that may be taken to assist an impaired colleague. If the person has a close relationship the impaired individual, then a conversation expressing concern, asking questions and offering support may be useful. If there is not a close relationship between the person who notices the impairment and the one who is impaired, then recruitment of a third party that has a close relationship with the impaired, and is willing to engage the impaired in a conversation, might be of benefit. If this is not an option, or if personal conversations with the impaired are unsuccessful, then some sort of formal "intervention" might be necessary. For students who are concerned about a colleague, this may involve a conversation with the Dean of students or a physician at the student health center.

DOCUMENTATION OF INSTITUTIONAL AND ACADEMICALLY-RELATED PUBLIC SERVICE

I. PHILOSOPHY AND GOALS OF INSTITUTIONAL AND ACADEMICALLY RELATED PUBLIC SERVICE

I am extremely lucky to work in an academic community, and in turn for that privilege, I believe that I should share my knowledge in learning experiences for others. The academic environment at MUSM offers many opportunities for faculty to guide and support one another in teaching and professional activities. The interdisciplinary nature of our curriculum challenges each faculty member to think beyond their science and to integrate their knowledge with that of other science and medicine faculty, as well as to develop skills in communication and cooperative engagement with colleagues and students. A strong sense of responsibility in stewardship of the curriculum is required to make our medical school function properly, and this stewardship is ultimately tied to citizenship at MUSM. I have upheld my responsibilities in stewardship in many ways, including participation in revising learning objectives, modifying examination questions in response to student performance outcomes, serving on medical school and university committees, and working to develop new learning tools for students that more effectively integrate basic science and medical concepts. My goal is to continue my stewardship of our curriculum, and to increase my assistance to other faculty members and participation in Division, School and University forums for constructive discussions that will enhance the academic and research environments of MUSM and Mercer University

In addition to my service on committees in the School of Medicine, I have participated in efforts to strengthen MUSM faculty relations inside MUSM and with colleagues around campus, to enhance the research environment, and to assist other faculty in research and teaching development at MUSM. I have attended nearly all Departmental and Medical School Faculty meetings and forums held for discussion of strategic plans, research, and medical school curriculum. I believe that the strength of MUSM, and Mercer University as a whole, rests in our ability to effectively work together. Mercer University is a small community, and it cannot function optimally unless all members participate in a constructive manner. The ability of MUSM faculty to cooperate and work with fellow Mercer faculty also affects the development of the Institution and the perception of MUSM by the community. On a larger scale, MUSM faculty members represent the School and the University through the quality of their research proposals, publications and presentations in the national and international arenas, as well as through their participation in peer-review activities, such as serving as a manuscript or grant reviewer. Thus, the Mercer environment must support scholarly efforts by the faculty and for faculty members to strive for quality in their professional endeavors. My goal is to devote more time to Mercer and Macon community activities, as I recognize that my contribution of time can cultivate relationships between MUSM and the Macon community and between MUSM and its larger University community.

II. SPECIFIC CONTRIBUTIONS/ACCOMPLISHMENTS

A. Service at the International Level

Organization	*European Journal of Neuroscience* (the official journal of the Federation of European Neuroscience Societies)
Description of Service	Invited Peer Reviewer
Date(s) of Service	Jan-Feb 2017; May-June 2017
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the *European Journal of Neuroscience* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

Organization	Austrian Science Fund
Description of Service	Invited Grant Reviewer
Date(s) of Service	April 2016
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the Austrian Science Fund to review a grant application, which involved providing feedback to the principle investigator regarding the scientific merit and significance of the application, and made a recommendation to the Austrian Science Fund as to whether the application should receive funding.

Organization	*European Journal of Pharmacology* (The official journal of the Federation of European Pharmacological Societies)
Description of Service	Invited Peer Reviewer
Date(s) of Service	2007-present (I've served as a reviewer for this journal 26 times since 2007)
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the *European Journal of Pharmacology* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published

Organization	*International Journal of Neuropsychopharmacology* (The official journal of the International College of Neuropsychopharmacology)
Description of Service	Invited Peer Reviewer
Date(s) of Service	August 2015
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the *International Journal of Neuropsychopharmacology* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

B. Service at the National Level

Organization	*Brain Research* (Journal)
Description of Service	Invited peer reviewer
Date(s) of Service	June-July 2017 April 2017
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the journal *Brain Research* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

Organization	Phar*macology, Biochemistry and Behavior* (Journal)
Description of Service	Invited peer reviewer
Date(s) of Service	January-February 2016 October 2015 January 2015
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the journal *Pharmacology, Biochemistry and Behavior* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

Organization	*Journal of Neurochemistry*
Description of Service	Invited peer reviewer
Date(s) of Service	February-March 2016 September 2015
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of *Journal of Neurochemistry* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

Organization	Handbook of Basal Ganglia Structure and Function, 2nd Edition (textbook)
Description of Service	Invited peer reviewer
Date(s) of Service	February 2015
Outcomes, Accomplishments, and/or Significant Impact	Prior to publication of the 2nd edition of the Handbook of Basal Ganglia Structure and Function, I was invited to review a chapter of this textbook and to provide corrections and editorial feedback to the authors of the chapter and the editors of the textbook.

Organization	*Basal Ganglia* (Journal)
Description of Service	Invited peer reviewer
Date(s) of Service	October 2014
Outcomes, Accomplishments, and/or Significant Impact	I was invited by the editor of the journal *Basal Ganglia* to review manuscripts detailing original research, and then provided the authors with feedback for improving their manuscript, and made recommendations to the journal editor as to whether the manuscript should be accepted and published.

Organization	American Society for Pharmacology and Experimental Therapeutics
Description of Service	David Lehr Award Task Force
Date(s) of Service	September-October 2013
Outcomes, Accomplishments,	As an invited member of this task force, I participated in the development of the guidelines for the David Lehr award, which is a grant that is now

and/or Significant Impact	offered by the American Society for Pharmacology and Experimental Therapeutics for qualified investigators.

Organization	Neurobiology of Motivated Behavior Study Section, Center for Scientific Review/National Institutes of Health
Description of Service	Invited research grant reviewer
Date(s) of Service	February 2013
Outcomes, Accomplishments, and/or Significant Impact	As an invited member of this study section, I reviewed R01, R03 and R21 grant applications submitted to the NIH. This involved providing feedback to the principle investigators and chair of the committee on the scientific merit and significance of each project that I reviewed, as well as discussing the viability of the projects I reviewed with other members of the study section.

C. Service at the Institutional Level

Organization	Chair, Neuroscience Faculty Search Committee, Department of Biomedical Sciences, MUSM
Description of Service	To organize and guide the committee in the search for two new neuroscience faculty members
Date(s) of Service	August 2017 (recently formed)
Outcomes, Accomplishments, and/or Significant Impact	We are currently in the process of reviewing applications, with the goal of performing our first round of phone interviews by the end of September.

Organization	Promotion and Tenure Committee, MUSM
Description of Service	I will review and assess promotion and tenure applications from members of the medical school faculty.
Date(s) of Service	August 2017 (recently elected)
Outcomes, Accomplishments, and/or Significant Impact	I will participate in reviewing applications for promotion and tenure beginning in October, and will be making recommendations to the Dean by mid-December.

Organization	University Strategic Planning Committee, Mercer University
Description of Service	As a member of this committee, I am participating in developing approaches to fulfill the President's goals as part of his strategic initiative to recruit, develop and retain qualified faculty and staff at Mercer University.
Date(s) of Service	May 2017-present
Outcomes, Accomplishments, and/or Significant Impact	We are in the process of developing specific parameters and strategies for identifying, recruiting, nurturing and retaining quality faculty and staff that embody the vision of Mercer University.

Organization	Grant Review Panel, MUSM
Description of Service	Co-Chair
Date(s) of Service	May 2017-present
Outcomes, Accomplishments, and/or Significant Impact	I've assisted in the design of this program to that seeks to improve the grantsmanship of our faculty by forming panels that review proposals and provide feedback to faculty before they are submitted for extramural funding.

Organization	Office of Admissions, MUSM
Description of Service	Non-committee interviewer
Date(s) of Service	October-December 2016
Outcomes, Accomplishments, and/or Significant Impact	I interviewed 4 applicants to the M.D. program at MUSM-Macon

Organization	Block 2 committee, MUSM
Description of Service	As a member of this committee, I helped guide and develop topics for Block 2 of the new medical school curriculum, which includes neurology, behavioral

	science, musculoskeletal and dermatology.
Date(s) of Service	April 2016-present
Outcomes, Accomplishments, and/or Significant Impact	Block 2 is divided into 4 4-week modules, and I was responsible for overseeing Module 2. I wrote the syllabus for this module, along with 14 cases for use in small group sessions, a facilitator guide for faculty, a monograph for students covering important material that was not described in the textbooks, organized and developed large group sessions, and wrote test questions for our weekly exams.

Organization	Assessment Sub-committee of the Curriculum and Instruction Committee
Description of Service	As a member of this committee, I participated in the development of assessment tools for use in the new medical school curriculum.
Date(s) of Service	August 2014-June 2016
Outcomes, Accomplishments, and/or Significant Impact	I participated in the development of new forms and tools for assessing student performance in small group sessions, and oral and written exams. I also participated in the adaption of the Angoff method for use in setting the standards for our summative written exams.

Organization	Chair, Masters in Preclinical Sciences Curriculum review task force
Description of Service	I tasked members with examining the scope of the curriculum in the masters in preclinical sciences program, and the viability of adding additional topics, such as neuroscience to the curriculum.
Date(s) of Service	June-September 2015
Outcomes, Accomplishments, and/or Significant Impact	Our task force investigation revealed that our MSPCS program curriculum was on par with Masters programs in preclinical sciences at other institutions, such as the Medical University of South Carolina and Tulane University School of Medicine. We determined that it would be advantageous to add Neuroscience material to the curriculum, but agreed that it would be best to wait until after the launch of the new MD to implement these changes.

Organization	Curriculum and Instruction Committee
Description of Service	As a member and Division of Basic Sciences representative of this committee, I participated in the development and implementation of the curriculum at

	MUSM.
Date(s) of Service	August 2010-June 2014
Outcomes, Accomplishments, and/or Significant Impact	I participated in the rotating review of phases and disciplines in the BMP curriculum, and the review and revision of our medical school competencies.

III. Membership in Professional Societies

I am a currently a member of the following national and international professional societies:

International Association of Medical School Educators (2015-present)

International Basal Ganglia Society (2010-present)

Sigma Xi Research Society, Mercer University Chapter (2009-present)

American Association for the Advancement of Science (2008-present)

American Society for Pharmacology and Experimental Therapeutics (2008-present)

Society for Neuroscience (1998-present)

As a member of the Society for Neuroscience and the American Society for Pharmacology and Experimental Therapeutics, I have repeatedly contacted members of the US Congress urging their support of bills proposing increases in the NIH budget, which would offer more research grant funding opportunities. As a member of the International Basal Ganglia Society, I have attended scientific meetings on an international scale, and have had the opportunity to interact with some of the top researchers in my field from all over the world.

Validation

Evidence of my sustained excellence in research, teaching and service that validates my value as a member of the faculty of MUSM may be found in my letters of reference, but are also described in greater detail herein.

I. Demonstration of sustained excellence in research

My area of focus in research is the molecular, behavioral and neurochemical alterations that occur in response to psychostimulant treatment, with a focus on the neural systems that underlie habitual drug abuse. This involves a detailed analysis of the changes in gene expression and neuronal activation in the basal ganglia and limbic system, and how these alterations relate to the behavioral phenotypes observed following psychostimulant treatment. The primary goal of my research has been and continues to be to understand the role that the patch-matrix system plays in the development and expression of repetitive and inflexible behaviors, which extends to habit formation and addiction. The goals of my two additional projects involve examining the ability of ketamine to reverse the depressive symptoms associated with psychostimulant withdrawal, and to examine neural mechanisms that underlie tic behaviors in Tourette syndrome. The findings from my research will increase our understanding of the deleterious effects of psychostimulant use and will shed light on the underlying neurochemical alterations that contribute to addiction and drug-seeking behaviors. Validation of my successful maintenance of a nationally recognized independent research program in addiction research is documented below.

Since being promoted to Associate Professor in 2012, I have published six papers in highly regarded and internationally recognized journals, such as *Brain Structure and Function*, *Neuropharmacology* and the *European Journal of Pharmacology*. I have presented data at seven national/international meetings, such as the Society for Neuroscience meeting, and the International Basal Ganglia Society meeting. Three of my students (two graduate, and one undergraduate) have presented their data as a representative of my laboratory at the Experimental Biology meeting (which is the annual meeting for the Federation of American Societies for Experimental Biology), with my undergraduate student winning second place in the undergraduate poster presentation competition sponsored by the American Society for Pharmacology and Experimental Therapeutics for her presentation of the role of patch-based mu opioid receptors in methamphetamine-mediated reward. I have also served as the thesis committee chairman/mentor for three Masters of Biomedical Sciences graduate students. I co-authored a chapter on transsynaptic regulation of basal ganglia gene expression in the Handbook of Basal Ganglia Structure and Function, 2nd edition, and authored a chapter on the epigenetic mechanisms and the therapeutic effects of fluoxetine (Prozac) in the textbook, *Fluoxetine: Pharmacology, Mechanisms and Potential Side Effects* (see **Validation Appendix**). I was invited to give a seminar at the University of Iowa to present my data on the mechanisms that underlie the neurotoxic effects of chronic methamphetamine exposure. I have secured NIH funding which spanned my time as an Assistant and Associate professor, and will likely receive NIH funding early next year for a new proposal that garnered very favorable reviews.

Together, these data support an evaluation of sustained excellence in research and the achievement of notable expertise in my field. My research is clearly well regarded by my peers as evidenced by my procurement of extramural research support, and the continued publication and oral presentation of my data in national and international venues. In summary, maintaining a successful research program, coupled with continuous publishing, funding and presentation of my data, indicate that I have demonstrated sustained excellence in research and scholarly activity.

II. Demonstration of sustained excellence in teaching

My area of teaching expertise is instruction in medical pharmacology/neuropharmacology/neuroscience in the Neurology, Brain and Behavior and Hematology phases (in the BMP curriculum, which ended in Spring of 2017) and Block 2 (in the new curriculum, which began in Fall of 2016). Validation of my sustained excellence in teaching in pharmacology and neuroscience can be found in my tutor evaluations, scholarly contributions to student instruction, and letters of reference. In the old BMP curriculum, I tutored and served as discipline resource faculty for ten years in the Neurology phase and for nine years in the Brain and Behavior phase. The pharmacology that was covered in Neurology, and that is now covered in Block 2, utilizes my knowledge of basal ganglia structure and function, monoamine pathways, and g-protein coupled receptor regulation and signaling mechanisms for teaching students the mechanisms of action of drugs used to treat Parkinson's disease and the receptors and signaling pathways of the autonomic nervous system and the mechanisms of action of drugs that act on this system. I also took over significant responsibility for a portion of the neuroscience material in the Neurology phase, serving as an instructor in the neuroanatomy wet lab, and delivering resource sessions on the motor system that were formerly taught by the neuroscience faculty, and this responsibility has carried over into Block 2. In order to provide improved interdisciplinary and clinically relevant coverage of the pharmacotherapies used for several psychiatric and neurological drugs, I authored a monograph that describes the neurobiological bases of the related disorders and phenomena, which was used as a primary reference in Brain and Behavior, and was revised for use in Block 2. For every portion of the curriculum that I am involved in, I regularly consult the Food and Drug Administration's website, (www.fda.gov), as well as the *Medical Letter,* which is a journal that provides peer-reviewed evaluations of new FDA-approved drugs, and new information on previously approved drugs, to ensure that the information (e.g., indications, side effects, toxicities) regarding the pharmacotherapies discussed are accurate and up-to-date.

I have also recently taken on significant curricular design responsibilities, as I am a member of the Block 2 committee, and was appointed to be the chair of Module 2 of Block 2 by the Block 2 committee chair (Dr. Tina Thompson). In this capacity, I wrote the syllabus for Module 2, designed/modified 14 clinical cases for use in the small-group patient-based learning sessions, and wrote a facilitator guide for faculty to use in conjunction with the clinical cases. I also was responsible for organizing the large-group team-based learning sessions, and delivered five of these sessions during Block 2. For three of these TBL sessions that I gave, I was solely responsible for the development the educational materials, which included readiness assessment quizzes, PowerPoint presentations, discussion questions for large group participation, and contributed material for the other two TBL sessions. As mentioned above, I continued to serve as an

instructor in the neuroanatomy wet lab, and wrote a monograph that was used as primary reference during Block 2.

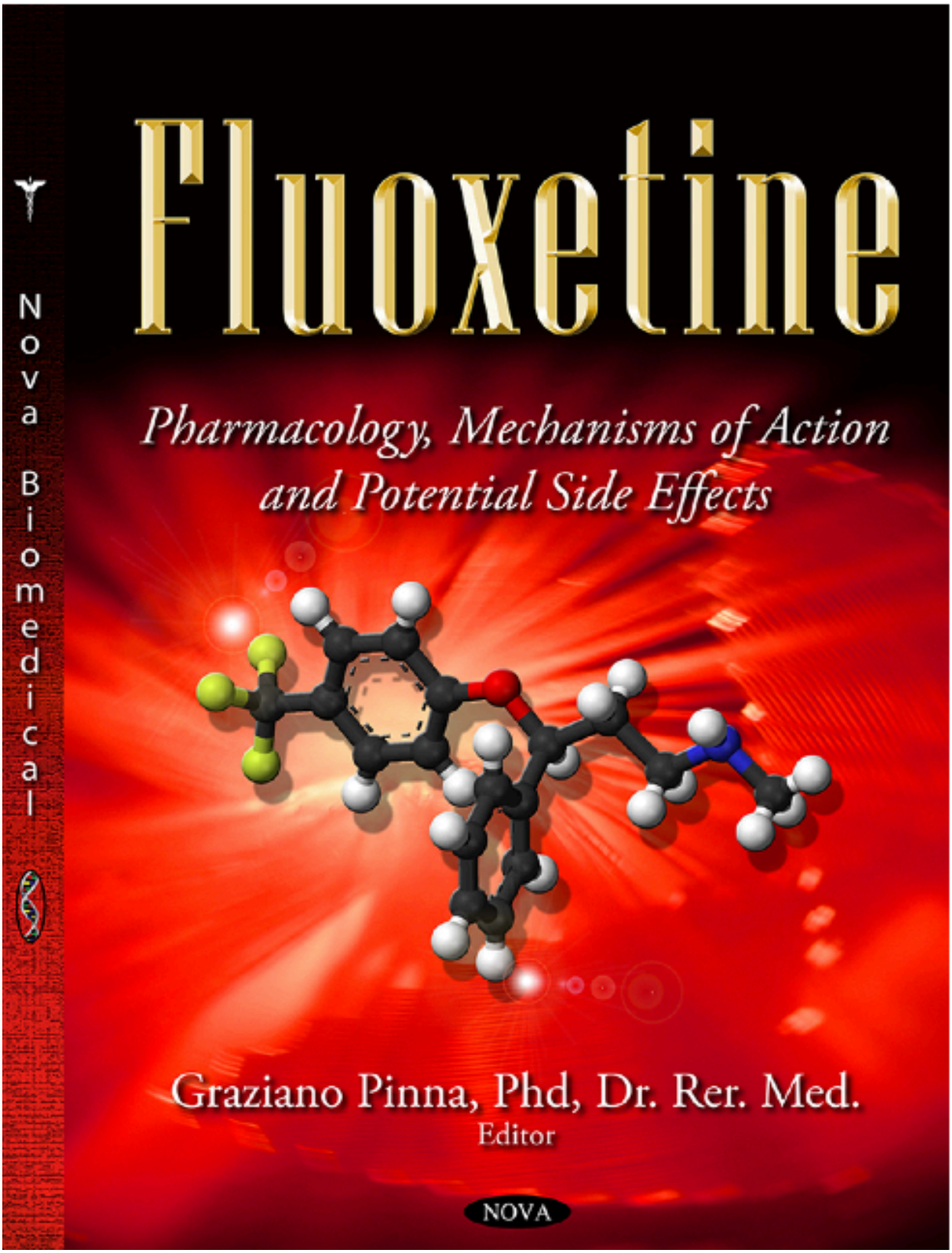
Together, these data regarding my continued dedication and effort in the development and delivery of the medical school curriculum, along with my consistently positive evaluations by my students show that I have demonstrated sustained excellence in teaching.

III. Demonstration of sustained excellence in service

At MUSM I have served on committees and participated in activities that promote collegiality, curricular development, and/or research. I served on the MUSM Curriculum and Instruction Committee until 2014, where I strived to represent the interests of the Division of Basic Medical Sciences (now the Department of Biomedical Sciences). I have recently been elected to the Promotion and Tenure committee for MUSM, and was called to serve on the University Strategic Planning Committee for Goal 2 of Mercer University's Strategic Plan in May of 2017. I am also currently the chair of the Neuroscience faculty search committee for MUSM. I also have served as a pre-clinical advisor for 13 medical students, and have mentored 3 Masters of Biomedical Science graduate students. I have also recently been appointed co-chair of a grant review program in the Department of Biomedical Sciences, which is aimed at improving faculty grantsmanship and funding in our department. I have also been involved in service on the national and international levels. I have served as an *ad-hoc* member of the Neurobiology of Motivated Behavior study section (part of the Center for Scientific Review/NIH) where I reviewed R01 proposals. I also served as a research grant reviewer for the Austrian Science fund. I have served as a peer reviewer for a number of national and international journals, such as the *European Journal of Neuroscience*, *Neuropsychopharmacology* and the *Journal of Neurochemistry*. I also participated (by invitation) in the development of the David Lehr award, which is a grant that is offered by the American Society for Pharmacology and Experimental Therapeutics (https://www.aspet.org/aspet/meetings-awards/aspet-awards/aspet-scientific-achievement-awards/the-david-lehr-award).

Together, these data showing my involvement in the activities described above indicate that I have demonstrated sustained excellence in service at the medical school, university, national and International levels.

IV. Validation Appendix



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Chapter 7

The Role of Epigenetic Mechanisms in the Therapeutic Effects of Fluoxetine and Other Selective Serotonin Reuptake Inhibitors

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Abstract

Epigenetics is the regulation of DNA transcription by DNA methylation, histone modification and non-coding RNAs, in the absence of alterations to the original DNA sequence that can be transmitted through generations. It is thought that epigenetic mechanisms play a role in the pathogenesis, as well as the treatment of major depression. SSRIs are among the most common compounds used for the treatment of major depression, and are also used as pharmacotherapy for several other psychiatric disorders. However, little is known about the potential epigenetic changes that are induced by SSRI treatment, how SRRI treatment may ameliorate the epigenetic alterations that are thought to underlie the pathogenesis of major depression or if these changes contribute to symptom relief. This chapter will review the recent studies on the epigenetic modifications that are thought to contribute to major depressive disorder and may occur as a result of SSRI treatment. For example, recent data show that SSRI treatment induces epigenetic modulation of gene expression including histone acetylation in the hippocampus, which is a region that is thought to be involved in the pathogenesis of major depression. In addition, these data suggest that epigenetic mechanisms may contribute to the persistent therapeutic effects of SSRI treatment.

Keywords: major depressive disorder, antidepressants, limbic system, brain derived neurotrophic factor, DNA methylation

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