COMPUTATIONAL ANALYSIS OF THE RESPONSE OF THE MONOAMINERGIC NEUROTRANSMITTER SYSTEM AND STRESS- AND SEX-STEROID HORMONE SYSTEMS TO ADMINISTRATION OF ANTIDEPRESSANT DRUGS

BY

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ABSTRACT

Fewer than half of depressed patients who take antidepressants experience complete remission of symptoms after 4-6 weeks of daily administration. The reason for this clinically observed heterogeneity in antidepressant response is still unclear. The majority of antidepressant drugs today are designed to enhance the brain's production of one or more of the monoaminergic neurotransmitters (serotonin [5HT], norepinephrine [NE], and dopamine [DA]). In order to better understand how the brain adapts to chronic antidepressant administration, we developed a computational model that represents the known interactions of the neurobiology of depression. This model was expanded with further knowledge extraction, and also re-structured as computational tools were improved. Our model is based on the neuroadaptation hypothesis, whereby the brain homeostatically adapts to chronic antidepressant administration by adjusting the strengths of transmitter-system components (TSCs) in order to return brain-region activity levels back toward their pre-drug baselines. The main finding was that the model can adapt through many different pathways, arriving at many different TSC-strength configurations but not all of the adapted configurations are also associated with therapeutic elevations in the monoamines. These results provide insight into the heterogeneity among individuals in response to chronic antidepressants. We expanded this model to incorporate the stress-hormone response and the male sex-steroid system, and postulated that if only a subset of adapted configurations to chronic antidepressant are therapeutic, then it is possible that individual, pairs, or subsets of TSCs are responsible for mediating the therapeutic state. Through several modes of analyses, including sensitivity, correlation, and linear temporal-logic, we found that therapeutic neuroadaptation to chronic antidepressant is an overdetermined process that depends on multiple TSCs, providing a potential explanation for the clinical finding that no single antidepressant alleviates depressive symptoms in all patients. Our models can be used to systematically facilitate the clinical practice of antidepressant augmentation by providing the means to computationally screen for antidepressant drug/hormone combinations that could potentially be more therapeutic than single drugs by themselves.

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In loving memory of Jose Guillermo Camacho

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CHAPTER 1: INTRODUCTION

"Because the [people] that don't know [about drugs], they talk about drug use as being simply like a, b, and c…that's like saying people are simply a, b, and c."

–Carl Hart, *Professor of Psychology, Columbia University.*

Carl Hart is known for his research in drug abuse and addiction, and was the first tenured African American science professor at Columbia University.

Our relationship with psychoactive drugs is undeniably highly intertwined with social conventions and personal situations and is hardly a simple subject. The duality of alcohol, for example, as both the staple of celebrations and the pitfall of alcoholics, illustrates the diversity of outcomes that drugs can have on different people who take them for varying lengths of time and under distinct circumstances. It is therefore essential to push the boundaries of our current understanding of how our brains respond and adapt to acute and chronic drug use. As chemicals or compounds that are taken into the body with the intention to produce some desired effect, most psychoactive drugs affect the brain by mimicking or displacing naturally occurring neurotransmitters. They can agonize or antagonize receptors, inhibit or enhance the release of neurotransmitters, or affect the activity of proteins that synthesize or break down neurotransmitters. Drugs that alter neurotransmitter levels or activity can alter neuronal interactions mediated by synapses, leading to detectable changes in the pre-drug firing-rates of neurons.

The brain responds to chronic drug use by adjusting the strengths of its neuron-specific receptors to restore neural activity to pre-drug levels. At the heart of the response to chronic drug use is the body's homeostatic adaptation to the persistent presence of the drug. But does everyone who takes a drug have the same pattern of homeostatic responses? Can different people adapt to the same drug by altering the expression or sensitivity of different receptors? Could this be why different people can be affected by chronic use of the same drug in different ways?

Heterogeneity in neuroadaptive pathways may underlie the large variability that is observed in chronic antidepressant drug effects. Although antidepressant drugs can cause changes in neurotransmission almost immediately after acute administration, it takes weeks to months for most of them to achieve therapeutic effects in depressed patients. This suggests that the acute

actions of antidepressant drugs on neurotransmission are not responsible for antidepressant effects. Instead, the therapeutic effect results from adaptation to chronic administration of the antidepressant, where the persistent adapted state is presumably different from the pre-drug state.

Unfortunately, not everyone who takes an antidepressant chronically has a therapeutic response. This leads us to speculate how some individuals neuroadapt to the same drug with therapeutic outcomes but not others. What neuroadaptive changes might be taking place in someone who neuroadapts therapeutically, versus someone who does not? Are there key proteins or receptors that could be mediating therapeutic neuroadaptation? Identification of key neuroadaptive factors could go a long way in designing antidepressant regimens that could result in more favorable (therapeutic) outcomes in more people. One of the largest challenges we face in answering these questions is the fact that neurobiological systems consist of a vast number of interacting elements that can neuroadapt in an immense number of possible ways.

In order to better understand the complicated process of neuroadaptation to chronic antidepressant, I used computational modeling to simulate and analyze possible interactions and processes that are involved in mediating antidepressant drug effects. This work resulted in two main findings. The first result of this work is the finding that different brains can neuroadapt to the same drug in many different ways, resulting in heterogeneous outcomes on neurotransmitter levels. This translates to the clinical finding that different depressed patients can have different outcomes with chronic administration of the same antidepressant.

The second result of this study was obtained from close analysis of therapeutic neuroadaption, which found that therapeutic outcomes following chronic antidepressant administration relies on contributions from all (not individual or pairs or subsets of) adaptable model units. The overdetermined nature of therapeutic neuroadaptation to chronic antidepressant supports a polypharmacy approach that targets multiple adaptable neurobiological elements to treat depression more effectively.

By computationally representing, simulating, and analyzing neuroadaptation to chronic antidepressants, this work is the first of its kind in depression neurobiology and provides a unique perspective that can markedly change the way we understand antidepressant pharmacology. The ideal outcome would be that this work leads to experimental verifications that in turn lead to the design of more effective pharmacological treatment options for the over 350 million people worldwide who are depressed (Kessler, Berglund et al. 2003).

1.1 BIOLOGICAL BACKGROUND ON DEPRESSION

Depression is a debilitating psychiatric disorder and a leading cause of physical disability and social strife (Greenberg, Stiglin et al. 1993, Cole and Dendukuri 2003, Kessler, Berglund et al. 2003, Holahan, Pahl et al. 2010, Greenberg, Fournier et al. 2015). Risk factors for depression include a family history of depression, past episodes of depression, female sex, and stress or trauma, among others (Kendler, Karkowski et al. 1999, Cole and Dendukuri 2003, Strine, Mokdad et al. 2008, Bravo, Dinan et al. 2014). Decades of research have amassed a huge dataset of neurobiological facts on the neurobiology of depression. It is known to involve disparate neural types located in various brain regions that release scores of different neurotransmitters onto a host of different receptor types. Despite this huge accumulation of facts, we still do not understand the neurobiology of depression. In consequence, we still do not know how to treat it effectively.

The monoamine hypothesis of depression has prevailed since the 1960s. According to the monoamine hypothesis, depression results from deficiency in one or more of the monoamines: dopamine (DA), norepinephrine (NE), and/or serotonin (5HT). Clinical observation in the 1960s showed that drugs known as tricyclic antidepressants (TCAs), which increase brain levels of DA, NE, and 5HT acutely, had antidepressant effects (Schildkraut 1965, Coppen 1967). The observation that the administration of Reserpine, a monoamine depleting drug, coincided with the onset of depressive symptoms, supported this view (Stein 1960). Antidepressant drug design since then has predominantly been based on this hypothesis. The monoamine hypothesis is consistent with findings that effective antidepressant drugs enhance monoamine neurotransmission (Scuvee-Moreau and Dresse 1979, Waldmeier 1982).

Unacceptable side effects of TCAs led to the development of antidepressant drugs targeting the monoamine neurotransmitter systems with greater selectivity. Antidepressant medications known as selective serotonin reuptake inhibitors (SSRIs) are currently the first-line pharmacological treatments for depression and are used by millions of people worldwide (Koenig and Thase 2009). Experiments on animals indicate that the main neurobiological effect of chronic SSRI administration is to increase brain levels of 5HT (Blier, Pineyro et al. 1998). However, evidence in humans suggest that there is considerable heterogeneity in the antidepressant response (Cunningham, Borison et al. 1994, Corrigan, Denahan et al. 2000).

SSRIs have fewer side effects than TCAs but still take weeks to months to produce any therapeutic effect and even then only provide relief in 35-50% of patients (Li, Li et al. 2014). SSRI-

nonresponders are usually treated either by switching them to another SSRI, or by prescribing a second drug (such as an antipsychotic, like Asenapine, or an atypical antidepressant, like Bupropion) to augment SSRI action on the monoamines (Fava and Rush 2006, Trivedi, Fava et al. 2006). Although these strategies have been shown to increase the proportion of depressed patients who respond to pharmacotherapy, an effective antidepressant combination unfortunately is never found in the 10-30% of depressed patients who are classified as treatment-resistant (Souery, Papakostas et al. 2006).

The low efficacy rate of SSRIs has sparked a high-profile controversy over whether or not SSRIs are reasonably more effective than placebo (Moncrieff and Kirsch 2015). Kirsch and colleagues conducted a meta-analysis that compared antidepressants with psychotherapy in placebo-controlled studies (Kirsch 2017). They found that members of the placebo group improved almost as much as the treatment group, and the authors concluded that the true drug effect (over placebo) was only 25% (Kirsch 2010). The authors posited that one factor that may be affecting the findings is the diversity of antidepressants in the clinical trials analyzed.

Kirsch and coworkers then conducted a meta-analysis that compared four different groups of antidepressants. However, the results across all four groups illustrated that no one group of antidepressants, including SSRIs, had a greater than 25% true drug effect (Kirsch 2009). Interestingly, it was observed that subjects who experienced negative side effects associated with antidepressant use had improved therapeutic outcomes over subjects who did not experience negative side effects. Kirsch and colleagues suggested that those subjects had a greater expectancy effect with antidepressant drugs because they experienced psychosomatic effects similar to the stated side-effects and subsequently anticipated an antidepressant effect (Moncrieff 2007, Kirsch, Deacon et al. 2008).

Other groups have proposed a different interpretation of this finding, namely that subjects who experience negative side-effects have increased sensitivity to the drugs over those who do not. This would correspond to a greater antidepressant effect in subjects who also experience negative side-effects. Kirsch and colleagues then combined both published and unpublished data from the Food and Drug Administration (FDA) for another meta-analysis, but only found less than a two-point difference between placebo and antidepressant using the Hamilton Depression Rating Scale, a questionnaire commonly used in clinical practice to evaluate depression severity. They found that the placebo was about 82% as effective as the real drug (Kirsch, Deacon et al. 2008,

Kirsch 2009). Kirsch and colleagues concluded by suggesting that alternative therapies, such as cognitive behavioral therapy and exercise, could be a better treatment choice for depression than antidepressant drugs (Kirsch 2010, Moncrieff and Kirsch 2015).

Interestingly, several groups have attempted to reproduce Kirsch's findings and have been unsuccessful. Statistical analyses conducted on the same data used in the Kirsch group's studies by other groups have not come to the same conclusions (Turner, Matthews et al. 2008, Fountoulakis and Moller 2011, Horder, Matthews et al. 2011). Still, the topic remains controversial and has led to several high-profile challenges against antidepressant efficacy (Fountoulakis, Hoschl et al. 2013).

Another controversy challenging current views on antidepressant pharmacology concerns Reboxetine, a selective norepinephrine reuptake inhibitor (NERI). Reboxetine is believed to bind the norepinephrine transporter protein (NET) and block the reuptake of extracellular norepinephrine into terminals, with low affinity for other reuptake blockers or receptors. A large number of studies have supported the belief that chronic administration of Reboxetine has antidepressant effects that are similar to or as effective as other antidepressants (Papakostas, Nelson et al. 2008). One report found that a combination of Reboxetine and exercise was an effective antidepressant intervention (Russo-Neustadt, Alejandre et al. 2004).

A recent meta-analysis challenges these findings and even suggests that in addition to being ineffective in the treatment of depression, Reboxetine can in fact be harmful for depressed patients (Eyding, Lelgemann et al. 2010). A recent survey combining data from several meta-analyses on Reboxetine concluded that different meta-analyses use idiosynchratic criteria for study inclusion, leading to divergent interpretations (Sepede, Corbo et al. 2012).

Many controversies surrounding the efficacy of current antidepressant drugs have led to rethinking of the monoamine hypothesis and motivated research into antidepressant drug design involving targets in addition to and beyond the monoamines (Berton and Nestler 2006). Importantly, controversies concerning antidepressant efficacy demonstrate the need to better understand antidepressant mechanism of action and design more effective interventions.

Chronic SSRI remains the first-line treatment for depression. Current understanding of SSRI mechanism of action is derived primarily from rodent studies, as similar acute and chronic pharmacological effects of antidepressants have been observed in both rodents and humans (Nord, Finnema et al. 2013). Acutely, SSRIs inhibit the 5HT transporter protein (5HTT) and increase 5HT

in the extracellular space as measured in rodents (Bymaster, Zhang et al. 2002, Koch, Perry et al. 2002). This activates somatodendritic 5HT1A autoreceptors on dorsal raphe nucleus (DR) 5HT-producing neurons. A decreased firing rate of 5HT neurons results, causing a subsequent decrease in 5HT release. The net effect of decreased reuptake due to SSRI and decreased DR firing-rate due to inhibition via 5HT1A autoreceptors is an increase in extracellular 5HT of 200% or more, depending on the SSRI (de Montigny, Chaput et al. 1990, Malagie, Trillat et al. 1995, Ceglia, Acconcia et al. 2004). This acute rise in 5HT is not enough to cause relief from depressive symptomology. Four to six weeks of maintained SSRI is required to achieve an antidepressant effect (Plenge and Mellerup 2003).

Under chronic SSRI in rats, 5HT neuron firing-rate returns to normal following desensitization of DR 5HT1A autoreceptors (Blier, Pineyro et al. 1998, Naudon, El Yacoubi et al. 2002, Gray, Milak et al. 2013). The consensus interpretation of this finding is that 5HT1A autoreceptors simply "tire out" with sustained exposure to elevated (200%) 5HT levels. The restoration of DR 5HT neuron firing activity (due to 5HT1A autoreceptor desensitization) coupled with 5HT reuptake inhibition (due to maintained SSRI) leads to greatly increased 5HT release. With chronic SSRI, extracellular 5HT rises above 400% of baseline in rats and is associated with depression relief (Ceglia, Acconcia et al. 2004). These findings led to the view that chronic SSRIs work by blocking 5HT reuptake and by causing desensitization of DR 5HT1A autoreceptors, which greatly elevates 5HT levels, which in turn results in an antidepressant effect (de Montigny, Chaput et al. 1990). There are a number of questions that remain unanswered by the current view.

Importantly, this perspective does not adequately explain why 5HT1A autoreceptors (on DR neurons) and 5HT1A heteroreceptors (on postsynaptic neurons) respond differently to chronic SSRI administration. Although 5HT1A autoreceptors have been found to desensitize with chronic SSRI, 5HT1A heteroreceptors in brain regions including the hippocampus do not, despite the fact that SSRI blocks 5HT reuptake and should elevate 5HT at all 5HT synapses (El Mansari, Sanchez et al. 2005). Why don't all 5HT receptors "tire out"? It also should follow from the current view that adding a 5HT1A receptor agonist would accelerate the antidepressant effect by enhancing the rate at which presynaptic 5HT1A autoreceptors desensitize, but current attempts at accelerating SSRI action through coupling with a 5HT1A receptor agonist have been ineffective (Blier and Ward 2003).

Figure 1 helps illustrate these unanswered questions and can be used to support an alternative neuroadaptation hypothesis of antidepressant response. It shows DR neurons inhibiting themselves through 5HT1A autoreceptors, inhibiting hippocampal CA3 neurons through 5HT binding to inhibitory hippocampal 5HT1A heteroreceptors, and activating prefrontal cortex (PFC) neurons through excitatory 5HT2A heteroreceptors (Azmitia, Gannon et al. 1996, Celada, Puig et al. 2013). When SSRIs inhibit 5HT reuptake and increase extracellular 5HT at all 5HT synapses including those onto hippocampal CA3 neurons, CA3 5HT1A heteroreceptors do not desensitize but DR 5HT1A autoreceptors do (de Montigny, Chaput et al. 1990, El Mansari, Sanchez et al. 2005). If 5HT1A receptors desensitized or "tire out" when exposed to sustained elevation in 5HT, then all 5HT1A receptors should desensitize equally, but that is not the case.

By inhibiting itself with its own 5HT via inhibitory 5HT1A autoreceptors, the DR regulates the 5HT level via negative feedback. When SSRIs are given acutely, the increase in 5HT in the extracellular space results in increased activation of the DR 5HT1A autoreceptor, decreasing the firing-rate of DR neurons and subsequently decreasing 5HT release through this negative feedback mechanism. However, single DR neurons also co-release glutamate along with 5HT (Johnson 1994, Gagnon and Parent 2014). Even if 5HT1A autoreceptor activation prevents chronic SSRI administration from unbalancing the system through large changes in 5HT levels, the decreased DR firing-rate would decrease the glutamatergic input from DR neurons to the CA3 and the PFC, changing their firing rates.

Because the PFC neurons do not receive as much glutamate from DR neurons as they did before SSRI administration, the PFC neuron firing-rate decreases, which in turn decreases the glutamatergic input from the PFC to the DR (de Montigny, Chaput et al. 1990). These changes disrupt the normal balance of activity between brain regions. My work suggests that DR 5HT1A autoreceptors may desensitize as part of a larger neuroadaptive process to restore unbalanced neuron firing-rates that result from SSRI administration, rather than through a "tiring out" effect from increased 5HT binding as suggested by the current view. My computational simulations and analyses show that the neuroadaptation hypothesis is also viable (see Chapter 3).

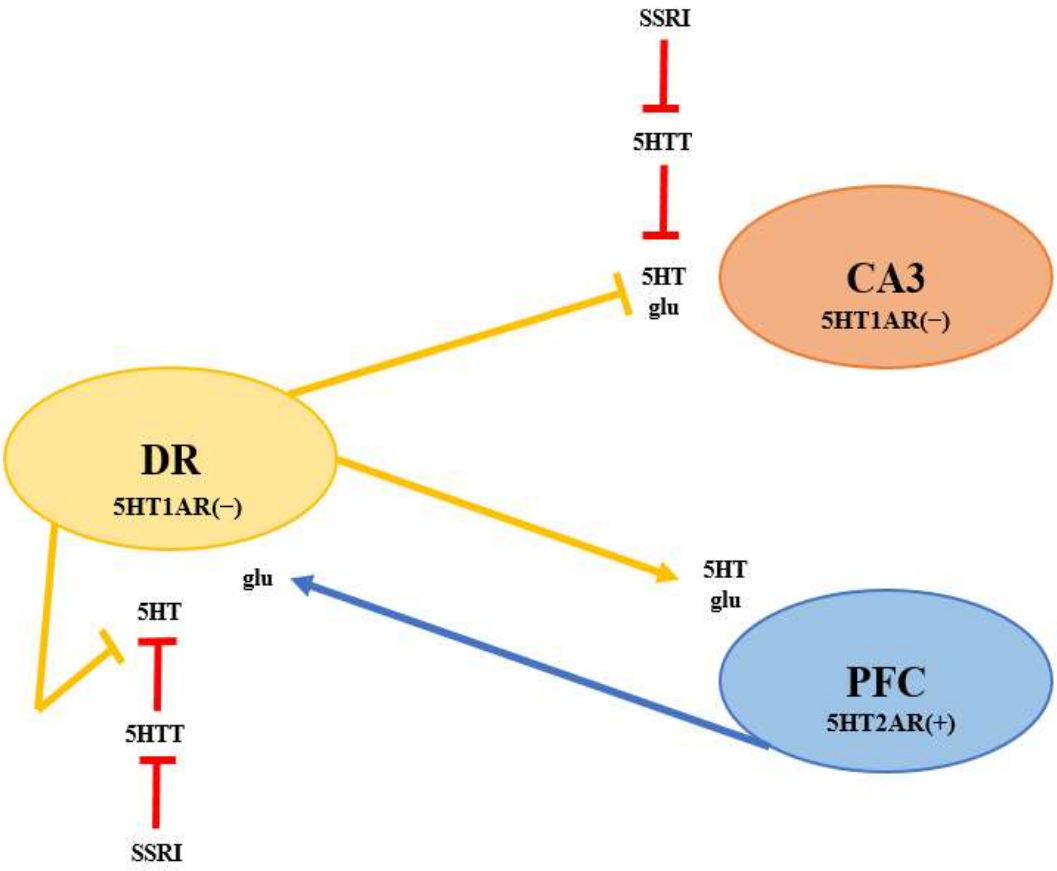


Figure 1: **Simplified representation of SSRI effects in the DR and interacting brain regions**. This schematic shows the DR projecting to the hippocampal CA3 region and the prefrontal cortex (PFC) with 5HT binding to inhibitory 5HT1A and excitatory 5HT2A heteroreceptors, respectively. Connections can represent synapses or other functional relationships. Arrows represent excitatory synaptic projections while tees represent inhibitory interactions between drugs and protein molecules, protein molecules and transmitters, or brain regions at synapses. In addition to 5HT, the DR also releases glutamate into CA3 and the PFC. Feedback inhibition onto the DR is mediated by 5HT binding to inhibitory 5HT1A autoreceptors. The PFC sends a glutamatergic projection back to the DR. The effect of an SSRI antagonizing the 5HT transporter (5HTT) molecule is indicated using blunt red arrows, which opposes the inhibitory action of 5HTT onto 5HT levels in the synapse. When SSRIs are administered acutely, 5HT levels increase and bind to the 5HT1A autoreceptor on DR neurons and decrease DR neuron firing rate, thereby reducing 5HT release. The figure shows that although 5HT elevations due to SSRI action are opposed by the decrease in DR firing rate, the glutamate levels in the CA3 and PFC are decreased with the reduced DR firing rate. As a result of the decreased glutamatergic drive of the DR onto the PFC the PFC sends less glutamate back to the DR, illustrating the disruption in the activity levels of all these brain regions. The schematic shows that the DR is central to the SSRI effect, and suggests that desensitization of the DR 5HT1A autoreceptor would be more effective in restoring neural system balance than desensitization of the DR CA3 heteroreceptor. It motivates an alternative explanation for DR 5HT1A autoreceptor desensitization with chronic SSRI administration as part of a process of neuroadaptation to restore neural-system activity levels rather than a "tiring out" process due to sustained elevation in 5HT.

1.2 BIOLOGICAL BACKGROUND ON STRESS AND DEPRESSION

Our current understanding of SSRI action is incomplete at best and likely involves interactions between the monoaminergic neurotransmitter system and other neurotransmitter or hormone systems. The most commonly observed risk factors for depression are stressful life events. Stress perturbs the physiological and psychological balance of an individual and leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis and elevated cortisol production (A.1: Overview of Stress, HPA Axis, and Cortisol). The relationship between the steroid hormone cortisol and depression has been studied extensively.

There is a large literature suggesting that cortisol is involved in both depression and the antidepressant response (Seckl and Fink 1992). The majority of depressed patients report a stressful life event precipitating their depression (Kendler, Karkowski et al. 1999, Caspi, Sugden et al. 2003). Although cortisol in the short-term may be adaptive and produce resiliency, chronic elevations in blood cortisol levels are related to depressive symptomology (Johnson, Kamilaris et al. 1992, Wong, Kling et al. 2000).

The serotonergic neurotransmitter system and the stress steroid system interact in many ways. For example, cortisol can alter expression of proteins involved in serotonergic synaptic transmission. Specifically, cortisol has been shown to decrease the expression of the 5HT1A autoreceptor on DR neurons and increase the activity of the tryptophan hydroxylase-2 enzyme (TPH2, 5HT synthesis enzyme), thereby increasing serotonergic tone (Fumagalli, Jones et al. 1996, Fairchild, Leitch et al. 2003, Manoli, Le et al. 2005). Also, activation of 5HT receptors in the paraventricular nucleus (PVN) of the hypothalamus can enhance HPA axis activity by inducing CRF release, but chronic antidepressant administration can reverse elevated cortisol levels due to stress (Pan and Gilbert 1992, Jensen, Jessop et al. 1999). A full understanding of antidepressant mechanism of action will require taking account of the interactions between the monoaminergic neurotransmitter and stress hormone systems (A.1: Overview of Stress, HPA Axis, and Cortisol).

1.3 BIOLOGICAL BACKGROUND ON SEX STEROIDS AND DEPRESSION

The stress- as well as the sex-steroids play a role in the etiology of depression. Women have twice the rate of depression as men, and there is a large body of evidence to suggest that women and men respond differently to antidepressant treatments (Young, Kornstein et al. 2009). Men and women differ in the pathophysiology of depression due to differences in the production

of gonadal hormones, specifically in the cyclical nature of estrogen and progesterone secretion in females and the more stable production of testosterone in males. Importantly, both men and women are at greater risk of depression following menopause and andropause, respectively (Rubinow, Schmidt et al. 1998, Rocha, Fleischer et al. 2005).

The sex hormones have been shown to be involved in monoaminergic (especially serotonergic) neurotransmission and the antidepressant response. For example, premenstrual syndrome (PMS) and perimenopausal depression involve interactions between estrogen and 5HT neurotransmission (Rubinow, Schmidt et al. 1998). Furthermore, estrogen is believed to affect monoamine neurotransmission so that the response to drugs that target the monoamines is altered in response to fluctuations in estrogen levels (Rubinow, Schmidt et al. 1998, Young, Kornstein et al. 2009). Testosterone supplementation has been found to alleviate depressive symptoms in both males and females in clinical settings (Orengo, Fullerton et al. 2005). Estrogen, progesterone, and testosterone receptors have been found in DR neurons, affecting the expression of genes involved in 5HT neurotransmission in both male and female rodents (Alves, Weiland et al. 1998, Robichaud and Debonnel 2005).

The results of several recent studies suggest that oral contraceptives may be causing depression in young women (Ross and Kaiser 2016). However, data from controlled clinical studies on the relationship between sex steroids and depression are limited and results have historically been inconsistent (Bottcher, Radenbach et al. 2012). For more details on the relationship between the sex steroids and depression, see A.2: Overview of the HPG Axis and Depression. The relationship between depression, the monoaminergic neurotransmitter system, and the stress- and sex- steroid hormone systems is incompletely understood and involves complicated interactions that should be taken into account in any framework designed to represent antidepressant action.

1.4 QUESTIONS WE WOULD LIKE TO ADDRESS

Why is the clinical antidepressant response so variable? How can we treat depression more effectively? Are there key factors mediating therapeutic responses to antidepressants? What is the relationship between depression and the stress and sex hormones? Would drug combinations, or combinations of drugs and hormones, be more effective than single drugs? Answers to these questions would go a long way toward alleviating depression in the 350 million people worldwide

who suffer from it every year, but this disorder defies easy answers. Due to its complexity, depression neurobiology cannot be understood without computational simulation and analysis.

The purpose of my dissertation work was to develop and use computational models of depression neurobiology to understand antidepressant action and the role of stress and sex hormones to suggest potentially more effective treatment strategies. We have created computational models of the known interactions between the monoaminergic nuclei, the stress-steroid system, and the sex-steroid system, and some related neurotransmitter systems associated with antidepressant action. These models differ in computational structure, and subsequent models are more neurobiologically extensive. With this work, we have provided potential answers to some of the questions we asked above. Our approach to answering all of these questions involves a combination of two computational modalities.

1.5 BACKGROUND ON COMPUTATIONAL MODELING IN NEUROBIOLOGY

Computer science has developed two different computational modalities by which to represent, simulate, and analyze systems (A.3: Difference between Imperative and Declarative Programming). They take the forms of imperative and declarative programming languages. In an imperative language a statement is a command ("do this"), while in a declarative language a statement is a fact ("this is true"). Imperative languages execute statements in a specified order whereas declarative languages can execute statements in all possible orders, thereby determining all possible consequences of the available facts. By elaborating the entire space of possible system states without limitations imposed by the order of commands, declarative languages can be used to provide a view of the range of model-system behavior much larger than what could be produced with imperative programming tools alone. Through their unique execution methods and capabilities, imperative and declarative languages can each provide unique contributions to our understanding of the outcomes of complicated neurobiological processes (Anastasio 2015).

The majority of computational models in neuroscience have been implemented using imperative programming languages, but declarative programming approaches have recently entered the realm of computational neuroscience. Maude is an example of a declarative language, developed at the University of Illinois at Urbana-Champaign, that has recently been used in computational models of normal and pathological neurobiological processes (Anastasio 2011, Anastasio 2013, Camacho and Anastasio 2017). Declarative processes can also be implemented in

imperative languages for computational efficiency. I have applied both imperative and declarative programming approaches in computational modeling of the monoaminergic neurotransmitter-producing system and important related neurotransmitter and neurohormone systems to expand our understanding of neuroadaptation to chronic antidepressant administration.

I have developed three computational models: the Monoamine-model (M-model), the Monoamine-Stress-model (MS-model), and the Monoamine-Stress-Sex-model (MSS-model). These models differ in extent: the M-model represents the interactions between the three monoaminergic transmitter systems and three non-monoaminergic transmitter systems; the MS-model includes these interactions but also incorporates the brain regions, hormones, and receptors involved in the stress response in addition to other transmitter systems; and the MSS-model includes the elements of the MS-model but also incorporates the hormones, receptors, and brain regions involved in the male sex-steroid system. There was not enough experimental data available to develop an analogous MSS-model of the female MSS system (see 4.6).

The models also differ in structure in that they took one of two structural forms: Region structure (M-model) or System structure (MS- and MSS-model). Briefly, the Region structure represents brain regions and transmitter systems as units, while the System structure represents all elements in the network (brain regions, transmitters, hormones, enzymes, etc.) as units. These different structural forms will be described in greater detail in Methods (see subsection 2.1). Analysis of these three models has provided insight into our understanding of chronic antidepressant response heterogeneity and proposes new pharmacological treatment options for depressed patients.

CHAPTER 2: METHODS

2.1 MODEL STRUCTURE AND FUNCTION

My thesis work involves elaboration of three computational models of depression neurobiology: the Monoamine-model (M-model), the Monoamine-Stress-model (MS-model), and the Monoamine-Stress-Sex-model (MSS-model). The models differ in extent (subsequent models incorporate more neurobiology) and take one of two different structures: Region structure or System structure. The models are nonlinear neural networks composed of interacting transmitter-system components (TSCs) representing the neurobiological elements of the transmitter and/or hormone systems they embody. In all cases, the same model is implemented in two programming modalities to exploit their complementary capabilities. One programming language is imperative (MATLAB®), while the other is declarative (Maude). Python™ is an imperative language that was used to implement declarative procedures in the MS- and MSS-model analyses. We used MATLAB to set model parameters and bring model behavior in line with experimental observation, to generate large sets of configurations of TSC strength adjustments, and to conduct sensitivity and pairwise correlation analyses. We used Maude for exhaustive search of adjusted TSC-strength configurations, and adapted Maude temporal-logic analysis into Python to study temporal relationships between TSC-strength configurations.

2.1.1 DESCRIPTION OF M-MODEL REGION STRUCTURE

The M-model has the Region structure. This structure takes the form of a recurrent neural network composed of six non-linear units that represent the three monoaminergic brain regions (DR, LC and VTA), as well as three non-monoaminergic neurotransmitter systems. The three non-monoaminergic neurotransmitter systems represented in this structure are the corticotropin-releasing factor (CRF), galanin, and glutamate systems. They are represented as tCRF, tGal, and Tglu, where t or T stands for “transmitter.” Each unit projects to every other unit including itself.

The monoaminergic units release their respective monoamines (DR releases 5HT, LC releases NE, and VTA releases DA) as well as other transmitters that they are known to co-release onto the other monoaminergic neurons. The non-monoaminergic units release only the one transmitter that they represent (e.g., the tCRF region only releases CRF) in this structure. The strengths of the projections of the non-monoaminergic units onto themselves, between each other, and from the monoaminergic units are represented as generic neural-network connection weights.

Unlike conventional units, the monoaminergic units can not only release more than one transmitter, but monoaminergic units can also have receptors specific for each transmitter they receive. Rather than having conventional connection weights, the connections onto the monoaminergic units in the model are implemented using the predominant receptors specific for each of the different transmitters released onto them. We define the predominant receptor as the receptor that mediates the main effect of a specific transmitter onto a specific neural type (e.g., the predominant receptor type for NE on DR neurons is the α1-adrenergic receptor (AR1)) (Baraban and Aghajanian 1980).

The connections onto the non-monoaminergic units in this structure are implemented using generic weights, because each non-monoaminergic unit represents a heterogenous set of neural types that have in common only that they all release the corresponding non-monoaminergic transmitter, and so the idea of a predominant receptor type on a specific neural type does not apply. Figure 2 is a schematic representation of the M-model, which has the Region structure. Table 1 shows all of the transmitters, receptors, and connection weights mediating the interactions between units in this model.

Each monoaminergic unit releases its transmitter(s) in an amount proportional to its activation level minus the transporter level for that transmitter. In addition to its receptor or generic

weight strengths, each unit also has a bias parameter. The units in the Region structure update by calculating their net inputs and "squashing" them; i.e., each unit computes the sum of its inputs (whether due to receptors [monoaminergic units] or generic weights [non-monoaminergic units]), adds its bias, and passes the result through the sigmoidal squashing function. Recurrent neural networks with a continuous squashing function are considered to be universal approximators and are widely used to simulate biological processes (Thomas R 1990, de Jong 2002). The squashing function bounds the activations of the 6 units between 0 and 1.

To evaluate unit activity with or without drugs, the activity of all units is set to 0, and the units are allowed to influence each other's activity for 150 time steps. Because the activities of the units in the model are prone to alternate and oscillate, activation of any unit is taken as the running average of its activity over the second half of the time step range (between time steps 75 and 150 inclusive). The running average of the oscillations of all units settles down to a constant value within 50 time steps. The alternating and oscillating behavior apparent for some of the units is expected due to the inhibitory self-connections of the monoaminergic units and asymmetrical

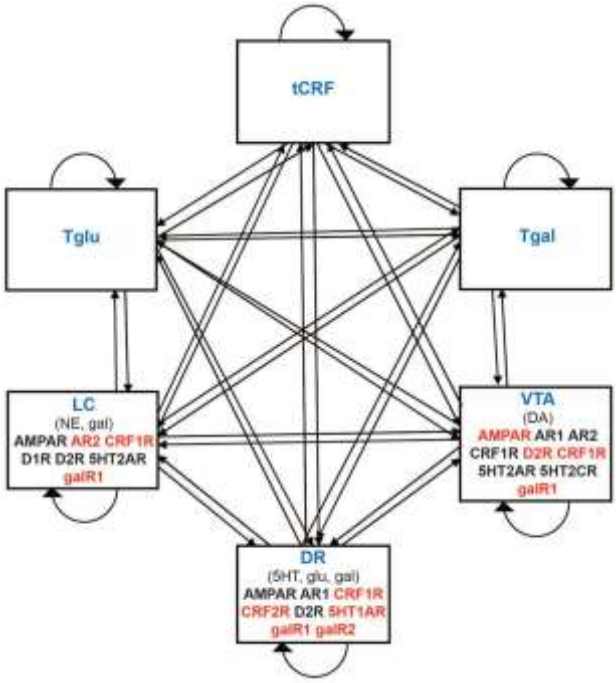


Figure 2: **Schematic representation of the monoaminergic neurotransmitter M-model.** The M-model has the Region structure. Each rectangle denotes a unit in the model that represents either a monoaminergic brain region or a set of regions that secrete a non-monoaminergic transmitter. DR, LC, and VTA (monoaminergic) refer to the dorsal raphe nucleus, locus coeruleus, and ventral tegmental area, respectively. tCRF, Tgal, and Tglu (non-monoaminergic) refer to corticotrophin releasing factor (CRF), galanin, and glutamate transmitter systems, respectively (t or T denotes "transmitter"). Connections between model elements can be excitatory or inhibitory and take the form either of the strengths of neurotransmitter-specific receptors (onto monoaminergic units) or of generic connection weights (connections onto non-monoaminergic units). Receptors mediating the predominant effect of each transmitter on the monoaminergic brain regions appear in their respective rectangles. Adjustable receptors (transmitter-system components, TSCs) are represented in red.

connections between the monoaminergic units (Luenberger 1979) and is in line with experimental observation (see B.1: Details on M-model Structure and Function).

From (across) / To (down)	**DR** 5HT gal glu	**LC** NE gal	**VTA** DA	**tCRF** CRF	**Tgal** gal	**Tglu** glu
DR	5HT1AR(−)	AR1(+) galR1(−) galR2(+)	D2R(+)	CRF1R(−) CRF2R(+)	galR1(−) galR2(+)	AMPAR(+)
LC	AMPAR(+) 5HT2AR(−) galR1(−)	AR2(−)	D1R(−) D2R(+)	CRF1R(+)	galR1(−)	AMPAR(+)
VTA	AMPAR(+) 5HT2AR(+) 5HT2CR(−)	AR1(+) AR2(−) galR1(−)	D2R(−)	CRF1R(+)	galR1(−)	AMPAR(+)
tCRF	wDR(+/−)	wLC(+/−)	wVTA(+/−)	wCRF(+)	wGal(+/−)	wGlu(+/−)
Tgal	wDR(+/−)	wLC(+/−)	wVTA(+/−)	wCRF(+/−)	wGal(+)	wGlu(+/−)
Tglu	wDR(+/−)	wLC(+/−)	wVTA(+/−)	wCRF(+/−)	wGal(+/−)	wGlu(+)

Table 1: Transmitters, receptors, and connection weights mediating interactions between monoaminergic units in the M-model. Interactions between the monoaminergic units (DR, LC, and VTA) are mediated by both excitatory (+) and inhibitory (−) receptors. A given monoaminergic unit is assigned one or at most two receptors for each transmitter it receives, which are the predominant receptors for the corresponding transmitter as determined through a comprehensive literature search (see text). Each monoaminergic unit may release more than one neurotransmitter onto another unit (listed in column headers), again as described in the literature. The non-monoaminergic units each release only one transmitter. They do not have receptors. Instead, the connections onto non-monoaminergic units from themselves, from each other, and from the monoaminergic units have generic connection weights. These weights are denoted by the letter "w" followed by a name associated with the sending unit (e.g., wDR is a connection weight from the DR unit while wGal is a connection weight from the Tgal unit). Note that all receptors and weights are unit specific (e.g., wDR takes different values onto tCRF, Tgal, and Tglu). The sign in parenthesis (+ or −) denotes the fixed polarity of a receptor or of a generic self-connection weight, while +/− means that the polarity of the corresponding connection weight is not fixed but can be set positive or negative during the parameter optimization process.

Drugs affect their targets through drug strength parameters. Agonist drugs add a contribution from a receptor equal to the product of the receptor strength and the drug strength. Antagonist drugs subtract a component equal to the product of the receptor strength, the drug strength, and the level of the cognate transmitter. Transporter blocking drugs reduce the level of a

transporter by an amount equal to the product of the transporter strength and the drug strength. Transmitter releasing drugs add a contribution of neurotransmitter to the unit activation level equal to the product of the amount of released transmitter (which is equal to the unit activation) and the drug strength. Drug strengths were limited to the range from 0 to 1 which appropriately limited their effects (see B.1: Details on M-Model Structure and Function).

2.1.2 DESCRIPTION OF MS- AND MSS-MODEL SYSTEM STRUCTURE

The MS- and MSS-models have the System structure. The System structure also takes the form of a recurrent network of non-linear elements. Importantly, in the System structure the units represent not only neurotransmitter-producing regions but also represent precursors, enzymes, transmitters, transporters, hormones, and receptors. The net input to each unit is passed through the sigmoidal squashing function to produce a squashed output state (as with the Region structure). Distinct from the Region structure, all parameters in the System structure are conventional neural-network weights, so all unit net-inputs can be updated efficiently via matrix multiplication of the unit state-vector and the weight matrix. The state vector represents the squashed output or state of each unit and the weight matrix consists of the weights of the interactions between the units.

Units could be categorized into input, output, and "hidden units." Input units do not receive connections from other units and can take on assigned values. Hidden and output units receive connections from input units and from each other. Output units are distinguished from hidden units in having targets (desired outputs). Hidden units have neither assigned nor desired values.

The connections between the elements represent the interactions between them. Findings on the interactions between the units were compiled via a comprehensive literature search. There are three classes of connection weights in the MS- and MSS- models: canonical, structure, and non-structure. Canonical weights are the weights of the connections between units representing key components of the MS or MSS systems, such as the weight from the DR to 5HT, representing the effectiveness of the DR in producing 5HT. There were 23 canonical weights in the MS-model and 36 canonical weights in the MSS-model (see B.2: MS- and MSS-model Canonical Weights). Structure weights are the weights of the connections between units representing neurobiological entities that are known to interact empirically, such as the weight from DR to galanin, representing the effectiveness of the DR in co-releasing galanin. Non-structure weights denote all other

connection weights; they may or may not represent as yet unidentified interactions that actually do occur neurobiologically. The three classes of weights are treated differently during model training.

Drugs in the System structure are represented as input units with connections to the model units that they interact with. For example, an SSRI is an input unit that sends an inhibitory projection to the 5HTT unit (because SSRIs inhibit the serotonin transporter). Figure 3 shows a highly simplified version of the MS-model, which has the System structure. The full diagram of

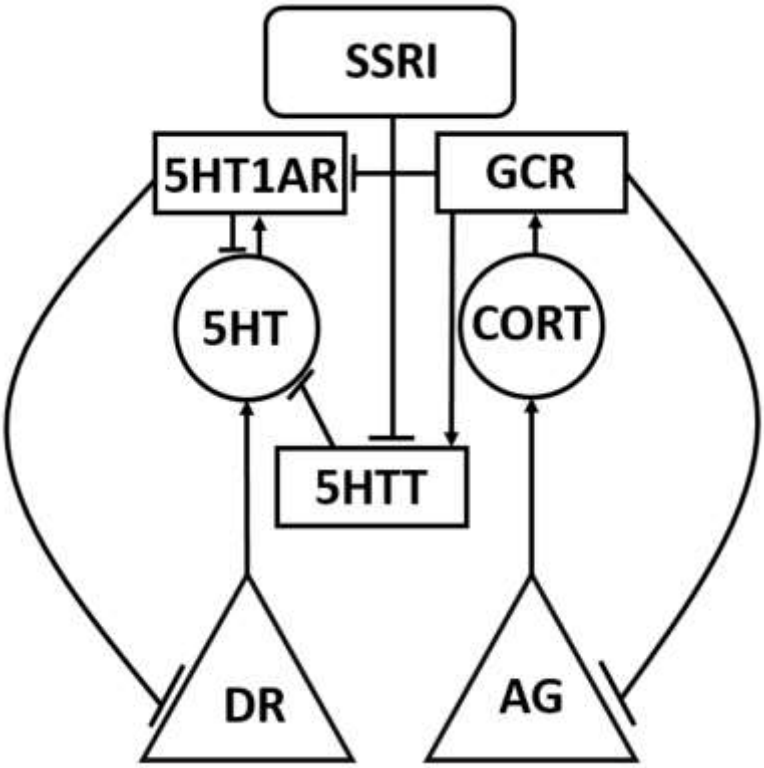
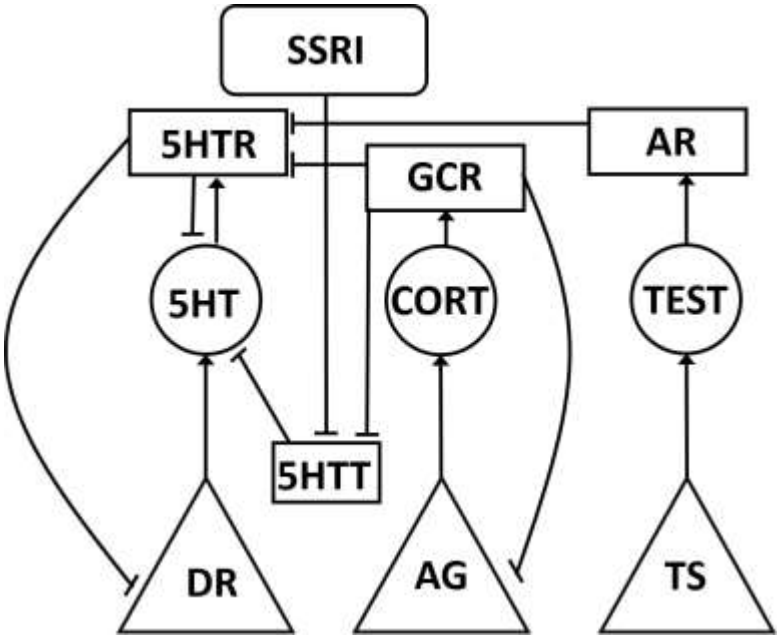


Figure 3: **Simplified schematic representation of the MS-model.** The MS-model takes the form of a recurrent neural network of non-linear elements (units) that represent neurotransmitter-producing regions, enzymes, neurotransmitters, hormones, and receptors. Each unit type in the model is represented using a different shape in this highly simplified model diagram, in which only one or two of each unit type is shown. Neurotransmitter and hormone producing regions are represented as triangles, neurotransmitters and hormones are represented as circles, protein molecules are represented as rectangles, and inputs are represented as rounded rectangles. Connections between model units can be excitatory (arrow) or inhibitory (tee). Abbreviations: dorsal raphe, DR; adrenal gland, AG; serotonin, 5HT; cortisol, CORT; serotonin transporter, 5HTT; 5HT1A receptor, 5HT1AR; and glucocorticoid receptor, GCR.

the MS-model can be viewed in the Supplemental Material of our MS-model paper (Camacho, Vijitbenjaronk et al. 2018). For more information on inclusion of specific units as structure or non-structure connections in the MS-model, see B.3: Details on MS-model Structure and Function.

The MSS-model, which also has the System structure, extends the MS-model to include the elements of the Hypothalamic-Pituitary-Gonadal (HPG) axis as units. Figure 4 is a highly simplified schematic of the MSS-model. The complete structure of the MSS-model can be found in the Supplemental Material of our MSS-model paper, and details on MSS-model structure connections can be found in B.4: Details on MSS-model Structure and Function (Camacho, Vijitbenjaronk et al. 2018).



2.2 IMPERATIVE MODEL TRAINING METHODS

2.2.1 IMPERATIVE TRAINING METHODS

2.2.1.1 GENETIC ALGORITHM

The M-model was trained using the genetic algorithm (GA) as implemented in MATLAB (see B.5: Details on GA Optimization of M-model). The GA essentially "evolved" the model parameter values so that model behavior "fit" with experimental observations. The parameters of the M-model are the receptor strengths, generic weights, bias levels, and drug strength parameters already mentioned, and also the efficacies of the monoaminergic transmitter transporters. Rather than maximize a fitness function, the GA was used to minimize an error function. The error function provided a measure of the difference between the behavior of the monoaminergic units in the model and that of real monoaminergic neurons in their responses to acute administration of various drugs. For the purposes of training the model the training data were assembled into an input/desired-output table or "truth table." The truth table is an array of input/desired-output

		Change in firing activity (%)		
		DR	**LC**	**VTA**
Drug or Combination	**Escitalopram**	−44	−45	−41
	Nomifensine	+50	−71	−39
	Reboxetine	0	−70	−31
	Trazodone	−40	25	0
	Asenapine	+17	0	0
	Aripiprazole	+48	0	0
	Bupropion	+100	−46	0
	Quetiapine	−43	+40	0
	Escitalopram+Aripiprazole	0	−26	N/A
	Escitalopram+Quetiapine	−65	+27	N/A

Table 2: **M-model truth-table.** This table shows the input/desired-output relationships obtained by the Blier lab for M-model training. Acute (2-day) administration of each drug or combination studied by the Blier group is present down the rows, and the corresponding percent changes in the firing activities of the monoaminergic nuclei (DR, LC, and VTA) are across the columns. The percent changes are represented as either increases (+) or decreases (−) from baseline activity. Cells with a 0 represent instances where no change was observed with acute administration of the input(s). In cases where experimental data was unavailable, the cell was labeled N/A.

training patterns that specifies how specific experimental manipulations, which are represented as patterns of desired network outputs, are known to affect specific neurobiological endpoints, which are represented as patterns of desired network outputs. In the M-model truth-table, the inputs are acute drug administrations, and the outputs are changes from baseline firing-rate of the monoaminergic neurons expressed as a percentage. The M-model truth-table was relatively simple and is represented below in Table 2 and graphically in Results.

Data used as the targets of optimizations (i.e., truth-table values) were derived from the work of Pierre Blier. The Blier lab studied acute (2-day) and chronic (14-day) antidepressant drug effects in male Sprague-Dawley rats using subcutaneous osmotic mini-pumps. Single-unit recordings from presumed 5HT, NE, and DA neurons in the DR, LC, and VTA, respectively, and others such as hippocampal CA3 neurons were made after 2 and 14 days. The error function includes data on eight drugs and two drug combinations as studied by the Blier lab using this protocol. The eight drugs and drug pairs are: Escitalopram, Nomifensine, Reboxetine, Trazodone, Asenapine, Aripiprazole, Bupropion, Quetiapine, Escitalopram/Aripiprazole, and Escitalopram/Quetiapine. The acute (2-day) effects of these drugs were used for model parameter optimization. For consistency in the M-model, only the drugs studied by the Blier lab under this specific protocol were included.

Descriptions of these drugs and their targets, along with references to the primary literature, are provided in B.6: Summary of Drugs and Drug Combinations Considered in the M-model. Through reduction of error, the GA optimized several criteria in addition to the agreement in the percentage changes in monoaminergic neuron activation levels due to acute drugs. These other criteria include the activation levels of the units in the absence of drugs, and the levels of the monoaminergic neurotransmitters in the absence of drugs or in the presence of the transporter blocking drugs Escitalopram and Reboxetine (See B.5: Details on GA Optimization of M-model). Of the 200 GA searches we ran, we selected the 10 lowest-error (i.e., most fit) parameter sets for further consideration (see 3.1.1).

2.2.1.2 GRADIENT-BASED MACHINE LEARNING

Due to the computationally intensive nature of the GA, the MS- and MSS-models were trained using a more efficient, gradient-based machine learning method (abbreviated GD, for gradient-descent). We were able to use GD to parameterize the MS- and MSS-models but not the

M-model because all elements in the MS- and MSS- models were represented as units. In the M-model, however, only the 6 transmitter regions were represented as units (see 2.1.1). The MS- and MSS-models were trained on baseline values and to reproduce data on the effects on neuron activations, transmitter, enzyme, and hormone levels of receptor blockade, lesions, and other experimental manipulations. All of the manipulations (drug or hormone administration, chemical lesioning, etc.) will be referred to as "inputs."

Data on the effects of inputs on model unit activations were obtained through an extensive literature search that compiled findings from multiple groups using a broad range of experimental methods. As for the M-model, the training data in the MS- and MSS-models were

		Desired output			
Row	**Input**	**DR**	**AG**	**5HT**	**CORT**
1	Baseline	0.50	0.50	0.50	0.50
2	SSRI	0.40		0.60	0.70
3	Dexamethasone			0.60	0.30
4	Stress	0.60	0.70	0.60	0.70
5	Adrenalectomy		0.30		0.30

Table 3: Simplified example input/desired-output dataset for MS-model. The relationships represented in this truth table are based on the simplified diagram in Figure 3. Each row represents the consensus of the results of one or more experiments in which output levels were measured in response to each input. Row 1 is the baseline where there is no input. In rows 2 and 3 the inputs are drugs: SSRI or dexamethasone (glucocorticoid receptor agonist). In rows 4 and 5 the input is stress or adrenalectomy. The output values range from 0.30 to 0.70, where 0.30 represents maximal decrease, 0.40 represents moderate decrease, 0.50 represents the baseline value, 0.60 represents moderate increase, and 0.70 represents maximal increase.

		Desired output			
Row	**Input**	**DR**	**Testosterone$_{end}$**	**5HT**	**CORT**
1	Baseline	0.50	0.60	0.50	0.50
2	SSRI	0.40	0.60	0.60	0.70
3	Stress	0.60	0.50	0.60	0.70
4	Testosterone$_{ex}$	0.60	0.70	0.60	
5	Stress+Castration			0.60	0.70

Table 4: **Simplified example input/desired-output dataset for MSS-model.** This table shows examples of the input/desired-output relationships obtained from the literature for model training. Each row represents the consensus of the results of one or more experiments in which output responses were recorded with each input. The output values range from 0.30 to 0.70, where 0.30 represents maximal decrease, 0.40 represents moderate decrease, 0.50 represents the baseline value, 0.60 represents moderate increase, and 0.70 represents maximal increase. The baseline endogenous Testosterone desired-output was set to 0.60 (instead of 0.50) to account for the higher Testosterone level in males than in females.

assembled into a truth table. Desired-output behavior was set using the findings of one or more different experiments from one or more different labs. The majority of the findings were derived from rodent studies but some were obtained from human, cow, or primate studies. Inputs are either present or absent (1 or 0) and outputs are assigned discrete levels between 0.30 and 0.70. Outputs could either decrease maximally, decrease moderately, have no change, increase moderately, or increase maximally, corresponding to desired-output values of 0.30, 0.40, 0.50, 0.60, and 0.70, respectively (see B.7: MS-model Truth-table Justification and B.10: MSS-model Truth-table Justification for a summary of the experiments included in the MS- and MSS-model truth-tables and corresponding references).

When more than one finding was available on a particular input-output relationship, a consensus agreement was found based on the available data. The MS- and MSS-model truth table was assigned discrete levels (distinct from the M-model truth-table, which used raw percentages obtained by the Blier group) in order to account for the differences in quantitative results obtained from a diverse range of experimental methods and research labs. It also allowed for consistency over the whole truth table. Table 3 and Table 4 are condensed, example MS- and MSS-model input/desired-output tables (i.e., truth table). For the complete truth tables, see B.9: Complete MS-model Truth-table and B.10: Complete MSS-model Truth-table.

The training procedure is an efficient, gradient-based machine-learning algorithm known as recurrent back-propagation (Pineda 1987). Briefly, the learning procedure begins by constructing a matrix of random initial weights. Then an input pattern (such as a drug or hormone administration, or a lesion) is chosen at random and presented to the network. The randomized matrix of initial weights and random order of training pattern presentation represent the two sources of randomness in the training procedure. The steady-state network response to the input is then found after 100 iterations of unit updating (state-vector/weight-matrix multiplication followed by net-input squashing). The Piñeda algorithm requires steady-state behavior and tends to train networks away from oscillatory behavior. The steady-state actual outputs are compared with the desired outputs specified by the truth table for the selected training pattern.

The differences between the desired and actual outputs of the units in the MS- and MSS-models are used to compute an error signal. Weight changes are calculated by propagating the error signal back through the network and through time for as many iterations as the network was updated to compute the output. Weight changes are scaled by a learning rate term. The learning

rates were set to 1 for the canonical and structure weights, and to 0.10 for the non-structure weights, in order to disadvantage the non-structure connections because they are not known for certain to be involved in the behavior being modeled. All weights had an upper-bound at absolute value 10. All weights had a lower bound of 0 except for the canonical weights, which had a lower bound of 1 to ensure they exerted an influence on overall network performance. For more details on training of the MS-model, see B.11: Details on Training the MS- and MSS-models Using GD.

After training, we pruned the networks in order to eliminate unneeded non-structure connections. This was intended both to minimize the number of non-structure connections and improve generalizability of model behavior. Generalizability was assessed by training the model on all single-manipulation inputs (e.g., single drug) and testing on all combination inputs (e.g., drug combinations). The process of optimizing the pruning method is discussed in detail in B.12: Pruning Methods. All further networks were trained using the following procedure: Networks with the full weight matrix (i.e. all canonical, structure, and non-structure connection weights) were trained on the full truth table (all single and combination inputs). Non-structure connections were pruned at the sensitivity cutoff optimized for generalizability, and the pruned networks were then retrained on the full truth-table.

2.2.2 NEUROADAPTATION PROCEDURES

2.2.2.1 BACKGROUND ON TSC ADJUSTMENTS

Most antidepressants are administered chronically, so models designed to represent the neurobiology of depression must represent the responses to chronic-drug as well as to acute-drug administration. All three models reproduce the effects of acute drug administration because they are included in the input/desired-output sets used in the training procedures of each model.

Additional computational procedures must be implemented to simulate the neuroadaptation that occurs in response to chronic drug administration. Neuroadaptation can occur in biological systems through changes in the “activities” (expression, sensitivity, cellular/synaptic localization, etc.) of key proteins (ion channels, transmitter receptors, etc.)(Turrigiano, Leslie et al. 1998, Desai, Rutherford et al. 1999, Turrigiano 1999, Turrigiano and Nelson 2000, Turrigiano 2008, Turrigiano 2012). It is the process by which the overall activity levels (specifically the resting or spontaneous activity levels) of neurons in key brain structures are brought back to their normative baselines under conditions of chronic perturbation.

The baseline, or normative, activity level of each unit in a non-adjusted (i.e. normative) network is its response when network input is 0 (no drug, hormone, lesion, or other input). Simulated administration of a drug alters the activation levels of the units in a model. Figure 5 compares baseline activity levels (dashed blue lines) of the units representing the 3 monoaminergic regions (DR, LC, and VTA), and the units representing 5HT and cortisol (CORT), with their

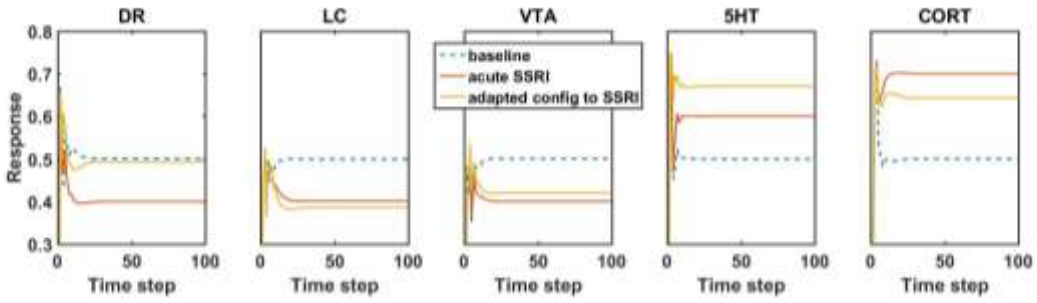


Figure 5: Representative comparison of model unit responses at baseline (no-drug), with acute (no-adaptation) SSRI administration, and with chronic (adaptation) SSRI administration in the MSS-model. The responses of the 3 key monoaminergic brain regions (DR, LC, and VTA), as well as 5HT and CORT, are shown in the subplots as labeled. In each subplot, the blue dashed line represents the baseline (no-drug) activity level of each unit. The red line in each subplot represents the responses of the units with acute (no-adaptation) SSRI administration. Note that the responses of the 3 key brain regions all decrease and the levels of 5HT and CORT both increase in the acute SSRI condition. The yellow line in each plot shows the adapted activity levels of each unit in one example adapted configuration with chronic SSRI administration. In this adapted configuration, the DR and VTA responses return closer to baseline, and 5HT and CORT responses increase and decrease, respectively.

responses to acute SSRI administration (orange lines). This figure was constructed using an MSS-model network, but is representative of the neuroadaptive principle as implemented in all three of our models. From the homeostatic viewpoint, drug-induced deviations from baseline activity can be interpreted as errors. We define the "activation error" as the sum of the absolute differences of the running average (M-model) or steady-state (MS- and MSS-models) neural-region unit activations (the 3 monoaminergic regions only (M-model and MSS-models) and the 3 monoaminergic regions as well as the paraventricular nucleus of the hypothalamus (MS-model)) from their baseline activations.

Neuroadaptation was simulated by allowing the model to adjust the strengths of a subset of transmitter-system components (TSCs) known to adjust with chronic administration of antidepressants (M-, MS-, and MSS-models) or stress (MS- and MSS-model only). These adjustments can be neuroadaptive under chronic antidepressant or stress in that they can bring the

activation levels of the units back toward their normative, no-drug or no-stress baselines. The neuroadaptation process is distinct from the neural network training procedure because in neuroadaptation, only a subset of the weights (specifically the 11, 10, and 13 adjustable TSCs in the M-, MS-, and MSS-models) are changing, and because the weights are not changing to produce agreement with the truth table but instead are adjusting to produce a more general overall restoration of the baseline activity of the neural brain regions.

In the M-model, which had the Region structure, all adjustable TSCs were receptors. Receptors were represented in the M-model explicitly as receptor-strength parameters that were receptor-type and neuron-type specific (e.g., the 5HT1A autoreceptor on DR). In the MS- and

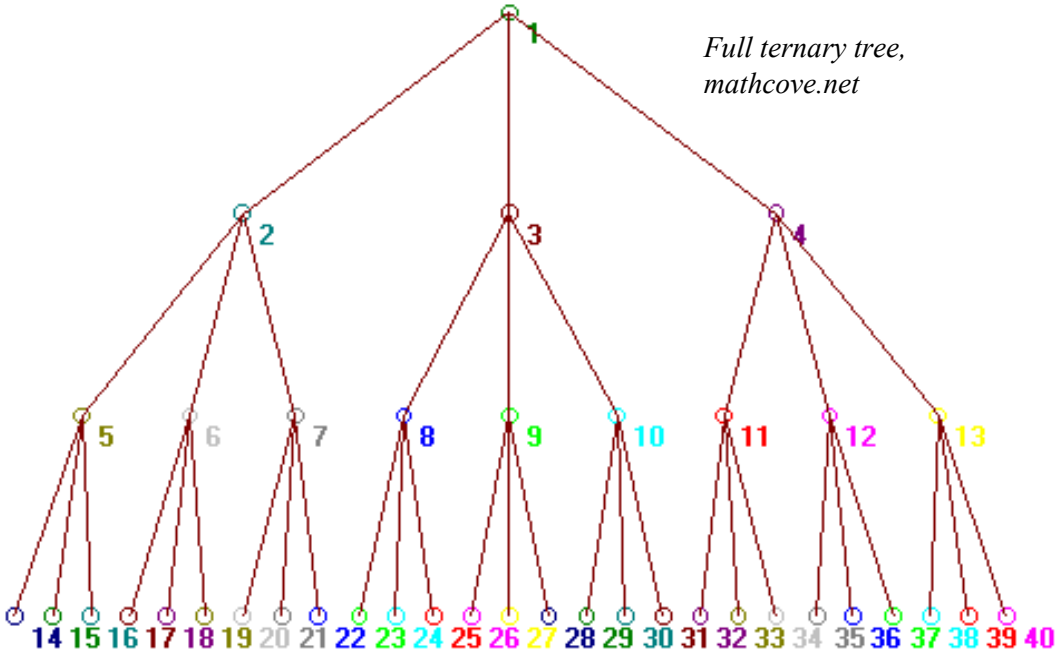


Figure 6: **Elaboration of a state transition tree.** This figure is a visual representation of the full set of adjustment pathways for a model with 3 receptors, any 1 of which can adjust on each adjustment step, and each receptor can make 3 adjustments total. The "depth" of the tree corresponds to the number of adjustments each receptor has made. Thus, all 3 receptors have adjusted once at depth 1, twice at depth 2, and so on. This tree has depth 3. The start state is depth 0. The number of adjusted states (receptor configurations) grows geometrically with depth. This relatively small "ternary tree" nevertheless illustrates how rapidly a tree of TSC adjustment pathways can grow. The M-model has 11 adjustable TSCs, each of which can increase or decrease by an increment at each adjustment step, for a total of 22 possible adjustments at each of 3 adjustment steps (depth 3). The MS-model has 10 adjustable TSCs, each of which can increase or decrease by an increment at each adjustment step, for a total of 20 possible adjustments at each of 6 adjustment steps (depth 6). The MSS-model has 13 adjustable TSCs, each of which can increase or decrease by an increment at each adjustment step, for a total of 26 possible adjustments at each of 6 adjustments steps.

MSS-models, which had the System structure, the adjustable TSCs were individual connection weights of cell-type specific TSCs (e.g., the weight of the connection from the 5HT1AR unit to the DR unit). Both representations will be referred to as "TSC strength." With each adjustment step, each of the adjustable TSCs can adjust by increasing or decreasing its strength by a specified increment (1 in the M and MSS-models, 0.50 in the MS-model) within the predetermined TSC strength minimum of 0 and maximum of |10| for the M- and MS-models and |5| for the MSS-model. These TSCs will be referred to as "adjustable TSCs." The models are agonistic as to whether TSC-strength adjustments are due to changes in expression, sensitivity, localization or a combination of these.

We define "initial error" as the adaptation error of a trained network subjected to chronic administration of a drug (or combination) in the absence of any adjustments of the strengths of the weights representing the adjustable TSCs. An "adapted network" was any network that, due to one or more adjustments in TSC weights, had an adaptation error lower than initial error. The responses of the canonical units in an example MSS-model network adapted to chronic SSRI are shown in Figure 5 as yellow lines. This figure shows that adaptation to an SSRI can return the responses of DR and VTA back toward normal while also increasing 5HT levels and decreasing CORT levels, which is in agreement with clinically observed chronic SSRI effects (de Montigny, Chaput et al. 1990, Ceglia, Acconcia et al. 2004, Dremencov, El Mansari et al. 2009, Ghanbari, El Mansari et al. 2010, Ruhe, Khoenkhoen et al. 2015).

Many other adapted networks, however, did not also have this pattern of adapted behavior. Transmitter and hormone responses to chronic drug administration, therefore, must be evaluated in many different TSC-strength configurations. We generated large sets of adjusted TSC-strength configurations for the M-, MS-, and MSS-models. Each model, depending on its number of adjustable TSCs and number of possible adjustments, had computed a different number of adjustable TSC-strength configurations.

Figure 6 is a visual representation of the tree of all possible TSC-adjustment sequences (pathways) for a model having only 3 adjustable TSCs. With only 3 adjustable TSCs and just 3 total adjustments for each TSC, this "full ternary tree" illustrates how large a fully elaborated tree with many adjustable TSCs and many allowed adjustments can become.

The number of possible TSC-strength configurations at any depth can be computed as $(2n)^d$, where n is the number of adjustable TSCs and d is the depth of the tree (or number of steps

in each adjustment pathway). The factor of 2 is included because each TSC can either increment or decrement at each level. We enumerated all possible configurations of the adjustable TSC weights that were reachable by increasing or decreasing any single TSC by a specified increment within predetermined bounds, for a present number of allowed adjustments (3 in the M-model, 6 in the MS- and MSS-models) that was the same for all weights.

Due to the randomness inherent in the GD neural-network training-method (see 2.2.1.2), equally well-trained networks can have very different network connection weights. This variability nicely corresponds to the natural variability in neurobiological properties that are known to occur between individuals (see 4.3). To account for this inter-individual variability, the MS- and MSS-models generated large sets of TSC-strength configuration starting from three representative networks, each trained from a different random initial weight matrix according to a different random order of input/desired-output presentations. In each of the 3 networks we made all possible combinations of 6 increments and 6 decrements in each of 10 (MS-model) or 13 (MSS-model) TSCs. Neuroadaptation in these models was studied by analyzing these large sets of adjusted TSC configurations (382,747 in the MS-model and 579,125 in the MSS-model). The inclusion of three representative networks in the MS- and MSS-models represents an advance over the M-model, which had only one representative case.

We explored TSC adjustment configurations in four principle ways. Two of these were implemented in MATLAB: we either followed single pathways through the tree, where the TSC adjustment at each step was chosen at random, or we computed the TSC-strength configuration at each step without following any adjustment pathways. The other was implemented in Maude or Python, where we exhaustively elaborated every possible pathway (full tree). Explicitly following TSC-adjustment pathways, whether singly or exhaustively, was useful for exploring the neuroadaptation process, but was computationally expensive. Computation of all possible TSC-strength configurations reachable in a set number of adjustments without explicitly following TSC-adjustment pathways was computationally cheaper and was useful for exploring the range of possible model behaviors.

The 11 adjustable TSCs in the M-model were the three monoaminergic autoreceptors: 5HT1A on DR neurons, α2-adrenergic receptor (AR2) on LC neurons, and dopamine receptor D2 (D2R) on VTA neurons; and specific receptors for CRF, galanin, and glutamate: galanin 1 receptors (galR1) on DR and LC neurons, galanin 2 receptors (galR2) on DR neurons, CRF1R on

DR, LC, and VTA neurons, CRF2R on DR neurons, and α-amino-3hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) on VTA neurons. The Blier lab (and others) found that these receptors adjust under chronic antidepressant treatment (Blier and de Montigny 1985, Blier and de Montigny 1987, Blier, de Montigny et al. 1990, de Montigny, Chaput et al. 1990, Haddjeri, de Montigny et al. 1997, Blier, Pineyro et al. 1998, Haddjeri, Blier et al. 1998, Dong and Blier 2001, Szabo and Blier 2001, Hawes and Picciotto 2004, Hawes, Brunzell et al. 2005, El Mansari, Ghanbari et al. 2008, Chernoloz, El Mansari et al. 2009, Chernoloz, El Mansari et al. 2009, Ghanbari, El Mansari et al. 2009, Borroto-Escuela, Narvaez et al. 2010, Ghanbari, El Mansari et al. 2010, Katz, Guiard et al. 2010, Ghanbari, El Mansari et al. 2012, El Iskandrani, Oosterhof et al. 2015, El Mansari, Manta et al. 2015, Wang, Li et al. 2016). The 10 adjustable TSCs in the MS-model and the 13 adjustable TSCs in the MSS-model correspond to actual TSC proteins that are known empirically to undergo adaptive changes under conditions of chronic manipulations within the purview of the model truth-table (see B.13: MS-model Adjustable TSCs and B.14: MSS-model Adjustable TSCs). The adjustable TSCs in both models are real TSCs that are known to play critical roles in the interactions between the three monoaminergic-transmitter systems and the stress hormone (MS- and MSS-model) and male sex hormone (MSS-model) systems.

2.2.2.2 IMPERATIVE PROGRAMMING NEUROADAPTATION EXPERIMENTS

2.2.2.2.1 M-MODEL

In the M-model, any 1 of the 11 adjustable TSCs could be adjusted up or down by 1.00 on each adjustment step. For example, one adjustment to desensitize the inhibitory 5HT1A receptor on DR neurons would bring the weight of the 5HT1A receptor on DR (3.10) closer to 0 by an increment of 1 (2.20) (TSC polarity was implemented in the unit update statements in the Region structure). The MATLAB version was used for making TSC-strength adjustments along single sequences (i.e., pathways) in which the TSC to be adjusted at any step was chosen at random. The adjustment was retained only if it resulted in a homeostatic reduction in activation error.

In separate computer experiments, 1,000,000 randomly ordered, strictly error-reducing sequences of adjustments (any 1 of 11 TSCs, adjusted either up or down by 1) were allowed to continue until further TSC strength adjustment produced no further reduction in activation error with chronic Escitalopram. We found that the majority of sequences (mode of the dataset) took 7 adjustment steps to reach “terminal” adaptation. The number of adjustments ranged between 2 and

26 with an average of 7.90 (see B.15: M-model Strictly Error-reducing Adjustments). Because these experiments continued until error could not be further reduced, they produced "terminally adapted" TSC strength configurations. We plotted 1000 configurations terminally adapted to chronic Escitalopram in B.15: M-model Strictly Error-Reducing Adjustments. This figure shows that there is not a single, unique, terminally adapted TSC strength configuration; in fact, there appear to be a multitude of heterogeneous configurations. To make definitive statements about neuroadaptation in the models it is necessary to examine sets of TSC-strength configurations that are complete in that every possible configuration is included. Technical limitations certainly did not allow examination of complete sets out to 26 adjustments. We were therefore limited to complete sets out to fewer adjustments which included terminally and non-terminally adapted TSC-strength configurations. We explored complete sets of non-terminally adapted TSC strength configurations using MATLAB, Maude, and Python.

2.2.2.2.2 MS- AND MSS-MODELS

Whereas representative adaptation pathways are important to simulate and analyze, it is also useful to precompute all possible TSC-strength configurations reachable along all possible pathways without explicitly following each pathway. The MS-model has 10 adjustable TSCs that can each adjust their strengths by an increment of 0.50 and the MSS-model has 13 adjustable TSCs that can each adjust their strengths by an increment of 1.

To find all possible adjusted configurations independent of adaptation pathway, we found all possible adjustments for all of the 10 (MS-model) or 13 (MSS-model) adjustable TSCs at each adjustment step, up to a total of 6 adjustments. Generation of the full set of TSC-strength configurations for a total of 7 adjustments was not possible due to computer memory limitations.

Note that the adjustable TSCs constitute a small number of the MS- and MSS-model parameters, but they are the only parameters whose values can change during neuroadaptation. Thus, an "adjusted network" was one in which the weights corresponding to the adjustable TSCs are replaced with adjusted values. Recall that the activation levels of the neural units change when a drug is administered. Different drugs or combinations will each impose different changes in the activation levels of network units, resulting in unique activation errors associated with acute administration of each drug or combination. Adjusted MS-model networks were considered adapted if their activation error was lower than their initial error, and adjusted MSS-model networks were considered adapted if their activation error was at least 25% lower than their initial

error. The MSS-model had a more stringent criterion because with 13 adjustable TSCs (versus 10 in the MS-model) the MSS-model had a much larger number of adjusted configurations. The monoamine and CORT levels due to administration of each drug, hormone, or combination were found for each adapted network and pooled and plotted in Results.

2.2.2.2.3 FULL-RANGE INDIVIDUAL-WEIGHT ADJUSTMENT (FRIWA)

We assume that all normal individuals will adapt to chronic antidepressant but we further assume that different individuals will adapt in different ways, and not all of them will achieve "therapeutic" levels of the monoamines, defined as the levels necessary to achieve remission of depressive symptoms (see 4.3). It is also possible that some adjustable TSCs contribute more to the attainment of therapeutic monoamine levels than others. We define "therapeuticity" as the ability of a TSC to contribute to the attainment of therapeutic monoamine levels through adjustments in its strength. We conducted full-range individual-weight adjustment (FRIWA) analysis (a kind of sensitivity analysis) to gauge the therapeuticity of single TSCs.

The starting configurations for FRIWA analysis were all of the configurations adapted to chronic SSRI that were also therapeutic, extracted from the exhaustive set of configurations of adjustments in all TSCs up to a total of 6 adjustments. Of the 382,747 (MS-model) and 579,125 (MSS-model) total TSC-strength configurations, the total number of adapted and therapeutic configurations over all 3 representative networks was 5598 (MS-model) and 12,351 (MSS-model). Therapeutic configurations were those that increased 5HT above the 5HT therapeutic floor (>=0.70) and decreased CORT below the therapeutic CORT ceiling (<=0.70). For more detail on therapeutic criteria, see B.16: Setting Therapeutic Criteria.

FRIWA analysis involved adjustment of the weight of a single adaptable TSC across its full range (0 to |10| (MS-model) or 0 to |5| (MSS-model); note that individual TSCs are either positive or negative), while the weights for the 9 (MS-model) or 12 (MSS-model) other adaptable TSCs remained frozen at their starting values, in each of the 5598 (MS-model) or 12,351 (MSS-model) adapted and therapeutic starting configurations. FRIWA occurred in steps, where each individual weight adjustment (IWA) was an increment of |0.50| (MS-model) or |1| (MSS-model). Thus, FRIWA generated a set of 200 new configurations (20 IWA adjustments for each of 10 TSC weights) starting from each of the 5598 adapted and therapeutic configurations for a total of 980,193 new configurations in the MS-model. FRIWA generated a set of 78 new configurations

(6 FRIWA adjustments for each of the 13 TSC weights) starting from each of the 12,351 adapted and therapeutic configurations for a total of 963,378 new configurations in the MSS-model.

All configurations that were no longer adapted after a step of IWA were excluded from further analysis, leaving 493,564 adapted TSC-strength configurations in the MS-model and 377,939 adapted TSC-strength configurations in the MSS-model. Of the 493,564 adapted MS-model configurations, 285,635 configurations were designated "resistant," because they remained therapeutic despite a step of IWA, while the remaining 207,929 configurations were designated "sensitive" because there were rendered non-therapeutic by a step of IWA. Of the 377,939 adapted MSS-model configurations, 354,462 configurations were classified as "resistant," because they remained therapeutic despite a step of IWA, while the remaining 23,477 configurations were classified as "sensitive" because they were no longer therapeutic following a step of IWA.

The weights of each of the 10 (MS-model) or 13 (MSS-model) adjustable TSCs in all of the post-IWA configurations were pooled over each representative network, and separated on the basis of resistance and sensitivity, excluding the weights that were manipulated by FRIWA. The mean weight of each adjustable TSC was computed for both the resistant and sensitive configurations of each network and compared (see 3.2.4). Further FRIWA analysis involved computing the pairwise correlations between all TSC weights over all the resistant, or over all the sensitive, configurations in each network (separately for each model). Only pairwise correlations that were statistically significant ($p < 0.05$) over all 3 representative networks of each model would have been reported in Results. Again for correlation analysis, the TSC weights that were manipulated by FRIWA were excluded.

2.3 DECLARATIVE PROGRAMMING METHODS

2.3.1 EXHAUSTIVE SEARCH IN MAUDE

Maude elaboration of adjusted TSC pathways was used in M-model analysis. Maude can generate the full set of possible TSC-strength adjustment pathways by making every possible sequence of TSC-strength adjustments (i.e., Maude elaborates the full tree of possible receptor-strength adjustment pathways) with simulated chronic drug administration. Maude can then search the space of all possible TSC-strength configurations by searching over the tree of all TSC-adjustment sequences (i.e., pathways). Each of the adjustable TSCs can either increase or decrease its strength by a specified increment. Because each adjustable TSC can potentially increase or decrease its strength at any adjustment step (increase or decrease is not allowed for TSCs at an

absolute strength of 10 or 0 for the M-model), there are potentially 22 different adjustments that can be made at any point along any pathway (i.e., at any depth in the sequence tree).

In Maude searches, TSC adjustments were allowed whether or not they reduced activation error. This allowed for the possibility that certain low error configurations could be reached only after passing through higher error configurations. Exhaustive search in Maude was limited to sequences of 3 adjustment steps in the M-model due to computational overhead. The Maude version of the M-model was used to characterize neuroadapted states with chronic drug or combination administration. All activation error values below the lowest activation error at depth 1 were considered to be "adapted" at all depths deeper than depth 1 with the M-model. Among the adapted TSC-strength configurations, we searched for configurations that achieved certain "therapeutic" levels of the monoaminergic transmitters. Therapeutic levels were based on clinical evidence concerning the therapeutic action of antidepressants (see B.16: Setting Therapeutic Criteria). Of primary interest are the monoamine levels associated with the adapted states of the model. In the MS- and MSS-models, monoamine levels were determined for TSC-strength configurations down to depth 6 by precomputation in MATLAB of all possible configurations.

2.3.2 TEMPORAL-LOGIC MODEL-CHECKING

2.3.2.1 THERAPEUTIC PATHWAY ANALYSIS

Elaborating actual adaptive pathways allows adaptation to be analyzed as a process. We studied the process of neuroadaptation by making allowed TSC weight adjustments (increments of 0.50 (MS-model) or 1 (MSS-model) up or down, within bounds of 0 and |10| (MS-model) or 0 and |5| (MSS-model)) in all possible sequences. Linear temporal logic (LTL) is a type of modal temporal logic which allows for reasoning about sequences of discrete states evolving in time. LTL analysis allows the evaluation of temporally specified logical propositions such as whether a specific state is always maintained or eventually reached; whether a specific state pertains only until another state pertains; or whether a specific state always leads to another specific state. Temporal-logic model-checking allows us to determine such temporal relationships between TSC-strength configurations (i.e. states).

We used LTL model checking to determine if specific degrees of neuroadaptation (e.g. a configuration in which a specific TSC has been adjusted down 3 times) always leads to an adapted and therapeutic configuration (for all possible sequences of adjustments proceeding from that

configuration up to a total of 6 adjustments) (see B.17: Details on Temporal-logic Model-checking Procedure for details on model-checking statements).

In order to evaluate model-checks in the MS- and MSS-models, it was necessary to define a set of logical predicates to be tested. The following predicates were used in the temporal-logic analysis: `fht_high`, 5HT is above the 5HT therapeutic floor (>=0.70); `cort_low`, CORT is below the therapeutic CORT ceiling (<=0.70); `TSC_sens_gt_3`, the adjustable TSC has sensitized by at least 3 steps; and `TSC_desens_gt_3`, the adjustable TSC has desensitized by at least 3 steps. Note that `TSC` in the last two predicates is a placeholder for any specific, adjustable TSC (e.g. 5HT1AR).

Then we evaluated the following propositions for each of the 10 (MS-model) or 13 (MSS-model) adjustable TSCs, where |-> and /\ are the LTL "LEADS TO" and "AND" operators, respectively:

```
TSC_sens_gt_3 |-> fht_high /\ cort_low
TSC_desens_gt_3 |-> fht_high /\ cort_low
```

These are equivalent to the LTL propositions that if at any point in the trajectory of TSC strength adjustments, the TSC sensitizes or desensitizes by at least 3 increments, then 5HT is high and CORT is low at some subsequent point in time. We found that both of these propositions were false for all of the tested TSCs in all 3 representative networks of both the MS- and MSS-models (see 3.2.6).

Next, we evaluated the following more-easily-satisfiable propositions, where \/ and ~ are the LTL "OR" and "NOT" operators, respectively:

```
TSC_sens_gt_3 |-> (fht_high /\ cort_low) \/ ~TSC_sens_gt_3
TSC_desens_gt_3 |-> (fht_high /\ cort_low) \/ ~TSC_desens_gt_3
```

These are equivalent to the LTL propositions that if at any point in the trajectory of TSC strength adjustments, the TSC sensitizes or desensitizes by at least 3 adjustments, then either 5HT is high and CORT is low at some subsequent point in time, or the TSC is no longer sensitized or desensitized. If 1 adjustable TSC was solely responsible for modulating the 5HT and CORT levels, then the model check for either of those 2 propositions for that specific, adjustable TSC should return True. Each LTL model check was carried out using each of the 3 representative networks

of the MS- and MSS-models for up to 6 adjustments, and only model-checking results that were consistent over all 3 networks are reported in Results.

Temporal-logic model-checking in Maude is ideal for these purposes because it allows us to determine temporal relationships between TSC-strength configurations (i.e., states). As a declarative programming language, Maude allows TSC adjustments to execute in all possible orders (see A.3: Difference between Imperative and Declarative Programming). For computational efficiency, we implemented Maude linear temporal-logic (LTL) model-checking procedures in Python and conducted a cross-check to confirm agreement between the two languages. Temporal-logic model-checking allows us to explore the temporal relationships between different adjustable TSC-strength configurations in a manner that is independent of the order of TSC adjustments (Monin and Hinchey 2003, Huth and Ryan 2004).

2.3.2.2 THERAPEUTIC CLUSTER ANALYSIS

We also used a form of LTL in the MSS-model analysis to examine the space of incrementally-adjusted TSC-strength configurations. If there are single or subsets of TSCs whose sensitization or desensitization is determinative of therapeutic states, then we would expect large and completely connected regions of adapted and therapeutic TSC-strength configurations within the space of incrementally changing TSC-strength configurations. However, if multiple TSCs contribute to the achievement of the therapeutic state, then we would expect there to be scattered or irregular regions of adapted and therapeutic states. We used the Henceforth LTL operator to search for connected regions of adapted and therapeutic states in which incremental adjustments of specific TSCs from therapeutic states always lead to subsequent therapeutic states. Each LTL and state-space analysis was conducted using each of the 3 representative networks for up to 6 adjustment steps, and only results that were consistent over all 3 networks are reported in MSS-model Results.

All hardware considerations are reported in B.18: Hardware Considerations.

CHAPTER 3: RESULTS

Although the M-model had a different structure and was trained using different methods than the MS- and MSS-models, all three models are based on a homeostatic hypothesis whereby the neural-region units in the network adjust the strengths of a subset of their TSCs in order to restore activity levels closer to no-drug, baseline levels with chronic drug administration. All three are models of the antidepressant response and are analyzed using both imperative and declarative programming methods. Results of the M-model are reported using one representative parameter set but the more efficient training method of the MS- and MSS- models allowed for reporting the results of three representative networks for each model. Overall, all three models illustrate that the clinically observed heterogeneity in the antidepressant response could reflect heterogeneity in adapted TSC-strength configurations that are usually associated with widely divergent monoamine levels. All three models provide predictions concerning the efficacy of drug or drug and hormone combinations that could potentially be more therapeutic than single antidepressants. Results from the MS- and MSS- models also provide insight into the therapeuticity (i.e., the ability to contribute to a therapeutic state) of different TSC types, through analysis of large sets of adapted configurations and temporal relationships between configurations that occur during the process of neuroadaptation.

3.1 M-MODEL (REGION STRUCTURE)

3.1.1 CHOOSING A PARAMETER VECTOR

Before the M-model can be used for analysis of adapted TSC strength configurations, its parameters must be set so that model behavior agrees with experimental observations on the acute effects of antidepressants (i.e., before any TSC adjustments take place). The GA was used to obtain 200 sets of M-model parameters that achieve this agreement with acute data by minimizing the RMS value of an error function (see 2.2.1.1). From the full set of 200 parameterizations, we selected the 10 best (lowest error) for further evaluation. We found that all elevated 5HT with acute Escitalopram administration (de Montigny, Chaput et al. 1990, El Mansari, Sanchez et al. 2005), all responded to acute Escitalopram with decreased DR unit activity (de Montigny, Chaput et al. 1990), and all elevated 5HT to an even higher level after adaptation to Escitalopram (de Montigny, Chaput et al. 1990, Invernizzi, Belli et al. 1992, El Mansari, Sanchez et al. 2005). When only the 5HT1A autoreceptor on DR was allowed to adapt, all desensitized this receptor to reduce activation error (de Montigny, Chaput et al. 1990, Naudon, El Yacoubi et al. 2002). One

parameterization was eliminated due to its aberrant adaptive behavior. The fit with the RMS error of 9.93 was selected for further analysis. It was considered to be a representative parameterization of the M-model because it had an error near the top of the error range (5.66 to 9.94 for the ten best) but still displayed the required adaptive capability (for more detail and figures on the GA parameterizations and selection of a representative parameterization, see C.1: Analysis of M-model Optimized Parameter Vectors).

3.1.2 CHARACTERIZING BASELINE (NO-DRUG) BEHAVIOR

Baseline activity of M-model units instantiated with the representative parameter set is shown in Figure 7A. All units settle into a stable oscillation about a constant offset following an initial transient. Such complex oscillation is in qualitative agreement with observation. Neurons in the monoaminergic nuclei, and in the non-monoaminergic regions with which they interact, can oscillate at multiple frequencies (Chergui, Suaud-Chagny et al. 1994, Gao, Liu et al. 2007, Zhang, Yang et al. 2008, Puig, Watakabe et al. 2010). The Blier lab also observed bursting behavior for some monoaminergic neurons depending on the neurons examined and the duration of drug administration (Katz, Guiard et al. 2010, Ghanbari, El Mansari et al. 2012, El Iskandrani, Oosterhof et al. 2015). We did not attempt to match real oscillation frequencies or bursting quantitatively with any of the three models because we were interested only in average unit activations (with the M-model) and steady-state neural-region unit activations (with the MS- and MSS-model) representing the overall activity level of each neural unit.

The responses of this network to acute Escitalopram administration are shown in Figure 7B. As with all drug conditions, the Escitalopram level is maintained over the course of the evaluation. Administration of Escitalopram changes the activation levels of the units including DR, LC, and VTA. This is consistent with experimental findings showing that acute administration of antidepressants can change the firing rates of neurons in those nuclei (reviewed in (Blier and El Mansari 2013)).

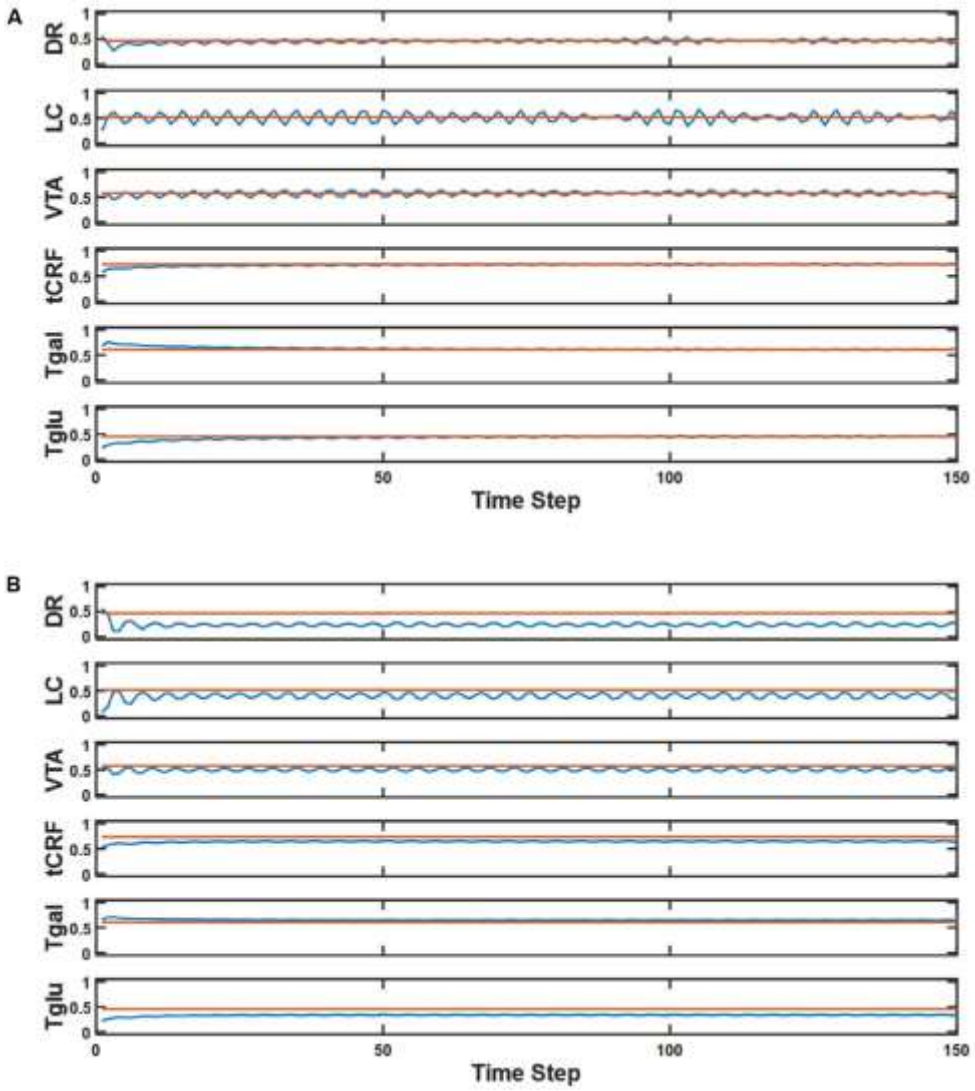


Figure 7: **M-model element activities in the baseline (no-drug) condition and acute (no-adaptation) Escitalopram condition**. (A) The blue line in each plot shows the activity of a different model unit across 150 time steps in the normal (no-drug) baseline condition. The superimposed red line is the average activity computed over the second half of the time series for the corresponding unit. These constant values for the normal condition are the baseline activations that define the normative activation of the network. (B) The blue line in each plot shows the activity of a different model unit across 150 time steps in the acute (no-adaptation) Escitalopram condition. The red line represents the average activity of each unit at baseline, plotting the same constant value as in (A). Of interest are the sustained levels of monoamine release, which is proportional to the average activity level of the monoaminergic units (DR, LC, and VTA). Oscillations apparent in the activities of some units are consistent with observation but are not relevant to model performance. Note that Escitalopram changes the average activity level of all of the units, and especially of the DR unit.

The activation levels of the monoaminergic units in the M-model instantiated with the representative parameter set with acute administration of all the drugs and combinations, expressed as percentage changes from baseline, are shown in Figure 8A (blue bars). The percentage changes

of actual DR, LC, and VTA units observed by the Blier lab under the acute influence of the same drugs and combinations (red bars) are shown for comparison. These plots, which are essentially graphical representations of the M-model truth table, demonstrate the M-model's ability to reproduce the data concerning the acute effects of antidepressant drugs on neurons of the monoaminergic neurotransmitter regions. This rather coarse level of agreement with the data or "fitness" is typical of GA parameterizations. Agreement between MS- and MSS-model performance and data using GD is closer by orders of magnitude.

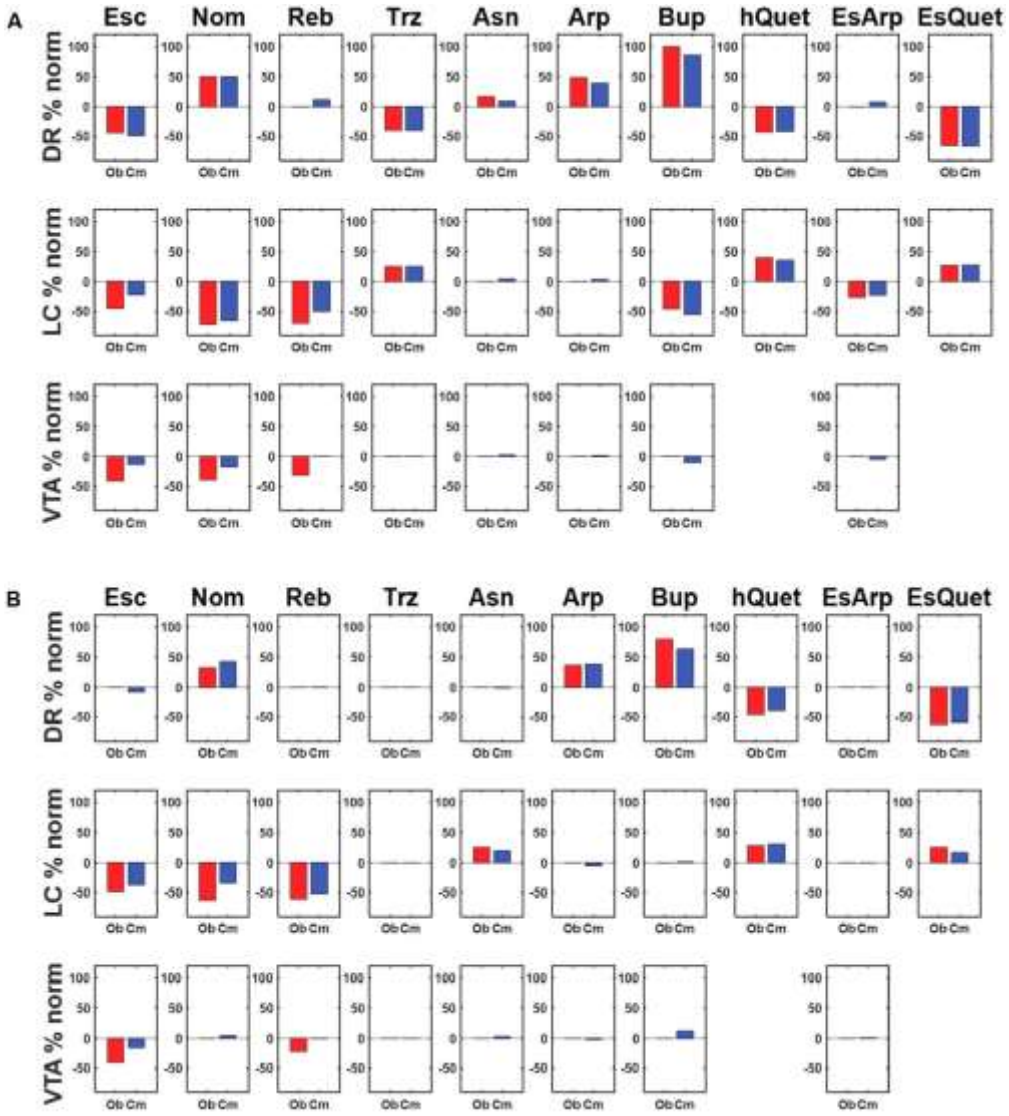


Figure 8: **Agreement between observed and simulated percentage activation changes following acute or chronic drug administration in the M-model** (A) Each row shows the percentage change from normal activation of the DR, LC, and VTA units, respectively, due to acute administration of the drug(s) in each column. The red bar represents the empirical value observed by the Blier lab, while the blue bar represents the computational value produced by the model. The model is parameterized using the representative parameterization (RMS error is 9.93, see text). (B) Each row shows the percentage change from normal activation of the DR, LC, and VTA units, respectively, in response to chronic administration of the drug(s) in each column. The red bar represents the value observed by the Blier lab. The blue bar represents the computational value produced by the model, each selected from among many adaptation runs for its agreement with the data (different runs produced different activation patterns; see text). The RMS error between the observed and computational values at the chronic stage is 9.58. Abbreviations: Escitalopram, Esc; Nomifensine, Nom; Reboxetine, Reb; Trazodone, Trz; Asenapine, Asn; Aripiprazole, Arp; Bupropion, Bup; Quetiapine, hQuet; Escitalopram + Aripiprazole, EsArp; Escitalopram + Quetiapine, EsQuet.

3.1.3 VERIFYING AGREEMENT BETWEEN THE MATLAB AND MAUDE VERSIONS OF THE M-MODEL

In addition to being used to optimize M-model parameters and for preliminary adaptation runs, the MATLAB program was used as a crosscheck for the Maude specification. Extensive crosschecking assured that the Maude and MATLAB versions of the M-model computed the same unit activations and transmitter levels in the no-drug and in all acute drug conditions. This validation step ensures that both versions of the M-model are consistent with each other and with the data on the acute effects of drugs on the activity of neural regions and the levels of neurotransmitters. Details on this validation step can be found in C.2: Verifying Agreement between the MATLAB and Maude Versions of the M-model.

3.1.4 CHARACTERIZING ADAPTIVE BEHAVIOR

To obtain a preliminary view of the adaptive capability of the M-model, only the DR 5HT1A autoreceptor was allowed to make adaptive adjustments. This preliminary evaluation was carried out using MATLAB, in which TSC-strength adjustments are made along a single pathway (i.e., a single sequence of TSC-strength adjustments). The DR 5HT1A could be adjusted up or down by 1 (or by a fraction, if its value was near the absolute-value limits of 0 or 10), and the adjustment direction on any adjustment step was chosen at random. An adjustment was retained only if it reduced activation error. These single-pathway adaptation runs show that desensitization of the DR 5HT1A autoreceptor decreases activation error and brings the monoaminergic unit activations back toward baseline (See C.3: Single-pathway Adaptation Runs in MATLAB).

In subsequent MATLAB adaptation runs, all 11 M-model adjustable TSCs were allowed to adjust (see Figure 8B) but did so one at a time along a single adaptive pathway. Both the TSC and the direction of adjustment (up or down by 1, or less to reach a TSC-strength limit) were chosen at random at each adjustment step, and an adjustment was retained only if it reduced activation error. The fully adjustable model was allowed to make 100 adjustment steps (only a small number of these actually reduced activation error). Each column in Figure 8B shows one specific adaptation run that was chosen for its agreement with the data. These runs show that agreement between M-model (blue bars) and observation (red bars) on changes in DR, LC, and VTA activation due to chronic antidepressant administration can be obtained with a TSC strength adjustment scheme based on neuroadaptation.

3.1.5 EXHAUSTIVE SEARCH OF ADAPTED STATES

We used exhaustive search in Maude to evaluate activation error and monoaminergic transmitter levels over all possible sequences of 3 TSC-strength adjustments, including pathways over which error could increase, producing all possible configurations of TSC strengths reachable within 3 adjustment steps with the M-model. Due to limitations in computational resources, exhaustive searches in Maude were limited to sequences of 3 TSC strength adjustments. The average number of adjustments to reach terminal adaptation (states in which further TSC-strength adjustments cannot further reduce activation error) with Escitalopram was found to be 7.90 (see Methods and B.15: M-model Strictly Error-reducing Adjustments). With 11 adjustable TSCs each able to increase or decrease its strength at each adjustment step, there would be 22^8, or over 54 billion, possible configurations reachable in 8 adjustment steps (see Methods). Exhaustive search on this order in Maude was not possible but search to level 3, which was possible, is highly instructive for three reasons.

First, it is unknown whether a state corresponding to terminal adaptation occurs in all rodents receiving chronic antidepressant treatment for 14 days (see 2.2.1.1), or in all humans over the course of a clinical trial (typically 6–8 weeks). Second, the GA-determined value of the DR 5HT1A autoreceptor (as well as the other 2 autoreceptors) in all of the 10 best parameter vectors in the M-model was just over 3, so exhaustive search to level 3 includes the 3-step, almost-complete desensitization of the DR 5HT1A autoreceptor (C.3: Single-pathway Adaptation Runs in MATLAB). Exhaustive search to level 3 is therefore appropriate for comparison of other adapted configurations to the configuration characterized by almost-complete DR 5HT1A autoreceptor desensitization, which is currently considered to be the main mechanism of SSRI effect (Blier, Pineyro et al. 1998, Gray, Milak et al. 2013). Third, exhaustive search avoids bias inherent in any kind of sampling of the configuration space, such as the sampling we did for illustrative purposes in MATLAB described in the previous subsection.

The results of the exhaustive searches in Maude with the M-model are reported in Table 5 in terms of the percentages of adapted TSC-strength configurations (i.e., states) that are also associated with therapeutic elevation in one or more of the monoamines. The percentages of adapted configurations that are also associated with therapeutic elevations in one or more monoamines are taken as M-model estimates of the percentage efficacies of the corresponding drug or combination. Although there are many adapted TSC-strength configurations, not all of these configurations are also associated with therapeutic elevations in the monoamines. Because

these percentages are considerably less than 100% in most cases, these results mirror the unideal antidepressant efficacies and heterogeneity between individuals in patterns of monoamine release following adaptation to the same chronic drug or combination that are observed in the clinic. The computational demonstration that the multiplicity of adaptable TSCs *implies* heterogeneity in monoamine levels in adapted configurations constitutes my proposed explanation for the low efficacy rates of antidepressants in depressed patients.

Row number	Drug(s)	Adap state	Number (percentage) of adapted states with therapeutic monoamine elevation						
			5HT	DA	NE	5HT/DA	5HT/NE	DA/NE	5HT/DA/NE
1	**Escitalopram**	655	192(**29%**)	0	0	0	0	0	0
2	**Nomifensine**	2463	2267(**92%**)	2463(**100%**)	1628(**66%**)	2267(**92%**)	1531(**62%**)	1628(**66%**)	1531(**62%**)
3	**Reboxetine**	1185	0	0	1185(**100%**)	0	0	0	0
4	**Trazodone**	296	0	30(**10%**)	54(**18%**)	0	0	6(**2%**)	0
5	**Asenapine**	63	0	0	0	0	0	0	0
6	**Aripiprazole**	706	0	0	0	0	0	0	0
7	**Bupropion**	1972	469(**24%**)	1972(**100%**)	1895(**96%**)	469(**24%**)	469(**24%**)	1895(**96%**)	469(**24%**)
8	**Quetiapine**	662	0	60(**9%**)	662(**100%**)	0	0	60(**9%**)	0
9	**Nomifensine + Escitalopram**	2462	2265(**92%**)	2462(**100%**)	1628(**66%**)	2265(**92%**)	1531(**62%**)	1628(**66%**)	1531(**62%**)
10	**Reboxetine + Escitalopram**	1218	355(**29%**)	1049(**86%**)	1023(**84%**)	309(**25%**)	294(**24%**)	889(**73%**)	260(**21%**)
11	**Trazodone + Escitalopram**	431	0	175(**41%**)	162(**38%**)	0	0	73(**17%**)	0
12	**Asenapine + Escitalopram**	132	2(**2%**)	0	74(**56%**)	0	0	0	0
13	**Aripiprazole + Escitalopram**	179	65(**36%**)	47(**26%**)	45(**25%**)	31(**17%**)	0	0	0
14	**Bupropion + Escitalopram**	2388	2308(**97%**)	2388(**100%**)	1760(**74%**)	2308(**97%**)	1717(**72%**)	1760(**74%**)	1717(**72%**)
15	**Quetiapine + Escitalopram**	586	66(**11%**)	204(**34%**)	586(**100%**)	0	66(**11%**)	204(**34%**)	0

Table 5: Exhaustive searches of adapted TSC-strength configurations with the M-model. The M-model was subjected to chronic administration of 8 drugs either alone or in combination with Escitalopram, and made every possible sequence of 3 allowed TSC strength adjustments. Initial error is the activation error due to the drug(s) before any TSC adjustments have been made. Adapted states (Adap state) expresses the number of TSC strength configurations (i.e., states) at depth 2 or 3 (i.e., after 2 or 3 TSC adjustments) that have activation error lower than the lowest depth 1 error. The other columns show the number of adapted TSC strength configurations (also expressed as a percentage of the total number of adapted configurations) that are associated with therapeutic elevations in one or more of the monoaminergic neurotransmitters. The therapeutic levels are >400%, >200%, and >200% of baseline for 5HT, NE and DA, respectively.

3.1.6 COMPUTATIONAL PREDICTION: AUGMENTING ESCITALOPRAM ACTION WITH SCH-202596, A GALANIN RECEPTOR BLOCKER

My hypothesis concerning the reason for the clinically observed heterogeneity in antidepressant response admits many options for experimental verification, including predictions involving specific combinations of compounds. Studies using pharmacological and genetic techniques have suggested that stimulation of the inhibitory galanin 1 receptor (galR1) results in a depression-like phenotype, while activation of the excitatory galanin 2 receptor (galR2) attenuates depression-like behavior (Lu, Barr et al. 2005, Rovin, Boss-Williams et al. 2012). These findings suggest that novel antidepressant drugs that target galanin receptor subtypes may be of potential therapeutic benefit.

We used exhaustive Maude search to take a closer look at the 5HT levels in adapted configurations to chronic Escitalopram, SCH-202596 (SCH, a drug that blocks galR1s), and the combination of both drugs. We found an increase in the percentage of adapted configurations also having therapeutically elevated levels of 5HT going from 29% (Escitalopram alone) to 78% when the SSRI and SCH were administered together. SCH by itself did not produce any adapted states with therapeutic 5HT levels. Recognition of the possibility that the brain has many ways to adapt to chronic antidepressant leads to the conjecture that certain combinations of drugs (particularly of receptor-blocking drugs such as SCH) could reduce the number of adapted configurations and, further, could channel the brain into a higher percentage of therapeutic states. Consistent with this conjecture, compared with Escitalopram by itself, the model shows that combining Escitalopram and SCH decreases the number of adapted states but increases the proportion of states with high 5HT.

Histograms of the number of TSC-strength configurations under chronic Escitalopram or Escitalopram/SCH that achieve different 5HT levels are shown in Figure 9A and Figure 9B, respectively. When the M-model was allowed to adapt to Escitalopram, the adapted configurations with therapeutically elevated 5HT were found across a fairly widespread distribution (Figure 9A). A visual comparison of the distribution of Escitalopram/SCH configurations to the M-model shows fewer adapted states with a smaller range that is pushed to the right toward high 5HT states (Figure 9B). Combining these two drugs not only increased the proportion of high 5HT states, but narrowed the 5HT-level distribution. The M-model predicts that the combination of Escitalopram and SCH could have higher percent efficacy for depressed patients than Escitalopram by itself.

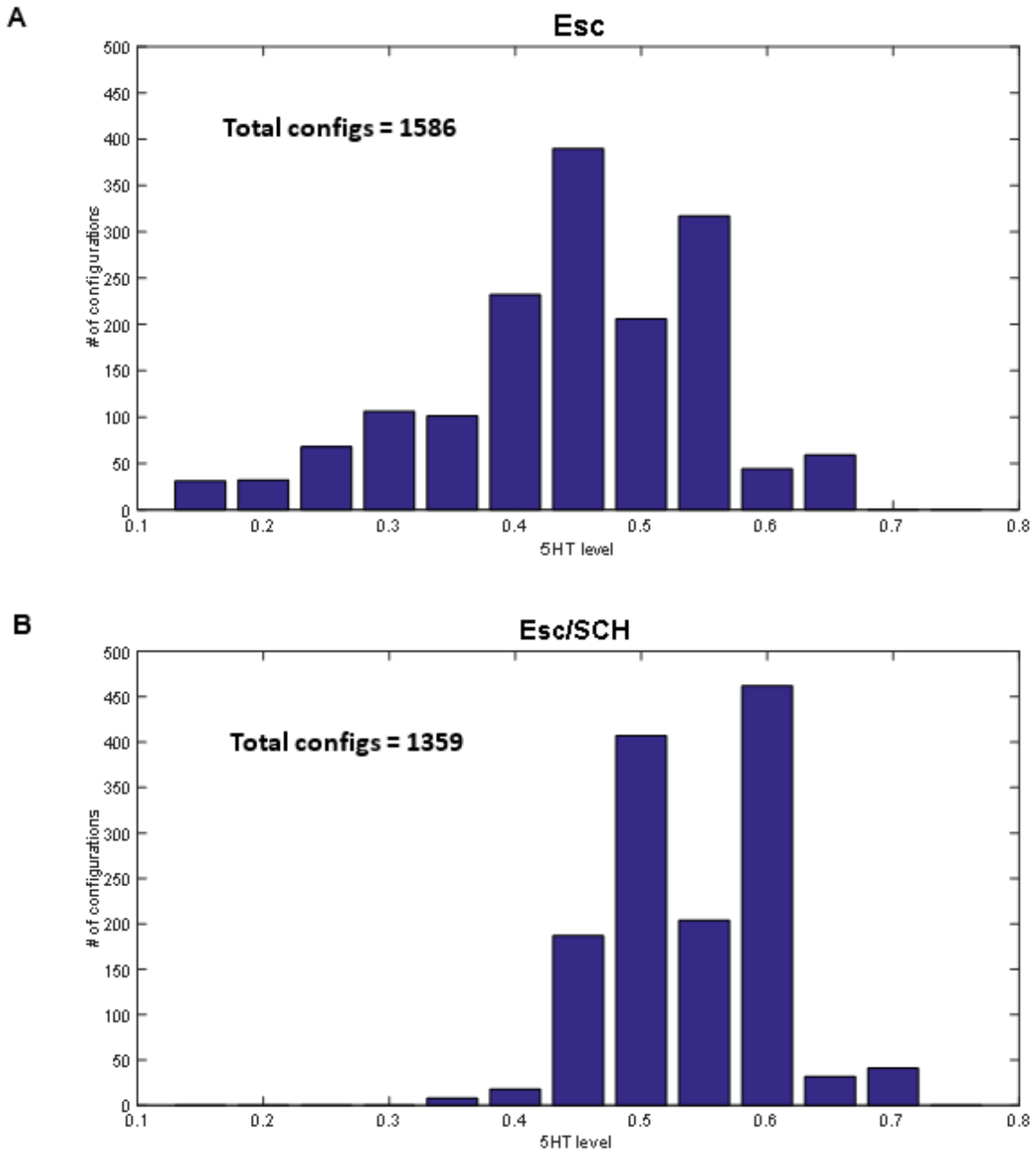


Figure 9: **Raw 5HT values of adapted configurations to (A) Escitalopram (Esc) and (B) Esc and SCH-202596 (SCH) using the M-model**. The 5HT levels are labeled along the x-axis and the number of configurations corresponding to each 5HT level are labeled on the y-axis. Total number of adapted configurations are labeled as "Total configs" in each case. Note the wide spread in the distribution of 5HT levels with Esc using the M-model. This figure illustrates that combining Esc with SCH not only decreases the number of adapted states (Total configs decreases from 1586 to 1359), but also shifts the distribution to the right with more therapeutic (high-5HT) states.

3.2 MS- AND MSS-MODEL RESULTS (SYSTEM STRUCTURE)

3.2.1 TRAINING AND PRUNING

MS- and MSS-model networks were trained, pruned on the basis of sensitivity, and then retrained as described in Methods. The results of the training method can be viewed in Figure 10 for the MS-model and Figure 11 for the MSS-model. Each plot in each of these two figures (Figure 10 and Figure 11) shows all of the actual and desired outputs for one brain-region, transmitter or hormone output unit (DR, LC, VTA, paraventricular nucleus (PVN) of the hypothalamus, 5HT, NE, DA, or CORT in the MS-model; testes and testosterone (TEST) were also included in the MSS-model figure). Each actual output response and desired output response is plotted as a solid line and a dashed line, respectively. Correspondence between steady-state actual responses and desired responses is nearly exact in both figures. The RMS errors over the networks shown in

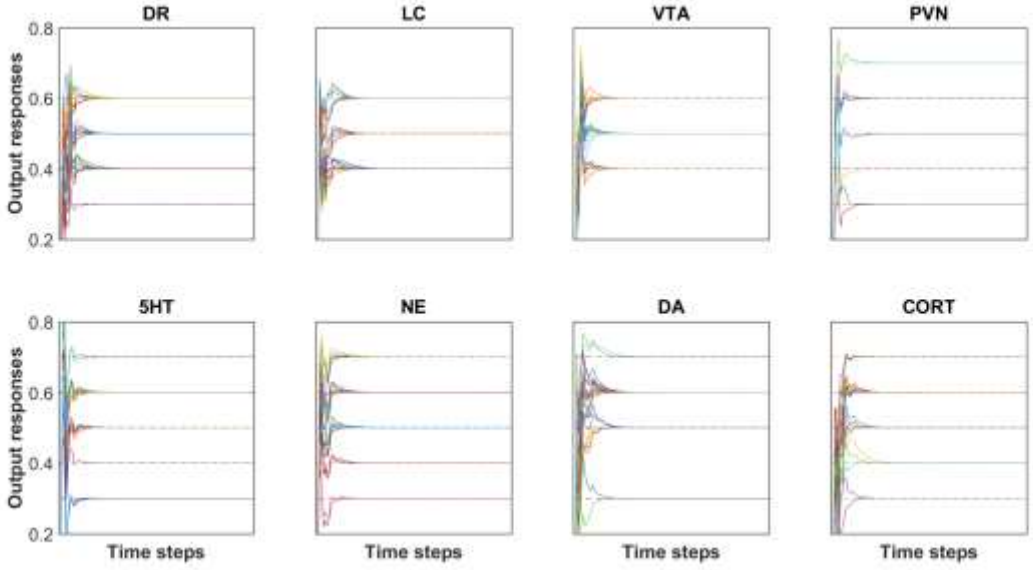


Figure 10: MS-model agreement between desired (i.e., target) and actual outputs after pruning and re-training. All of the desired and actual outputs, collected over all input/desired-output patterns, are represented in a single plot for each of the brain region and transmitter or hormone output units (DR, LC, VTA, PVN, 5HT, NE, DA, and CORT). Each output response is plotted as a solid line and each target (i.e. desired) output is plotted as a dashed line. Each of the outputs reach a steady-state value within 25 time steps. The RMS error of this network is 5.10×10^{-5}. Note that the solid line (actual output) is superimposed on the dashed line (desired or target output), illustrating the accuracy of the training method.

Figure 10 and Figure 11 was 5.10×10^{-5} and 1.84×10^{-4}, respectively. Comparison of these two values with the RMS error of 9.93 for the representative M-model parameterization indicates that the GD improves model agreement with data by many orders of magnitude (see 4.1).

The heatmaps in C.4 illustrate the extent of MS- and MSS-model agreement for all output units over the whole training set both before (A-C of each figure) and after pruning (D-F of each figure).

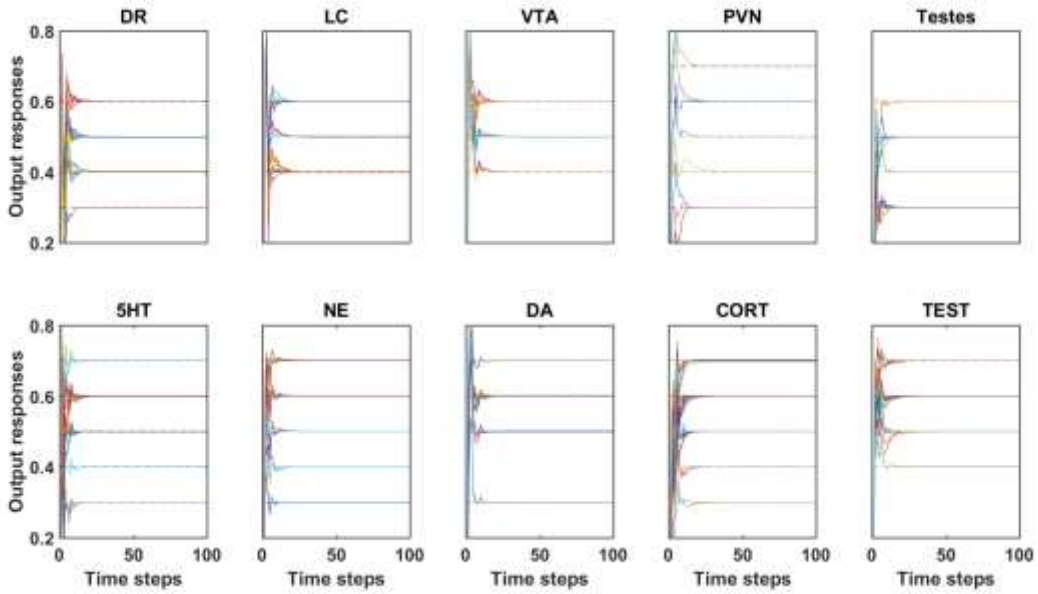


Figure 11: MSS-model agreement between actual model outputs and desired outputs after pruning and retraining. Single plots compare the desired (i.e., target) outputs with the actual responses of model output units representing monoamine or hormone producing regions, or the monoamines or hormones themselves (DR, LC, VTA, PVN, Testes, 5HT, NE, DA, CORT, and TEST). Actual or desired outputs are plotted as solid or dashed lines, respectively. All of the outputs reach steady-state within 25 time steps. The RMS error of this network is 1.84×10^{-4}. Note that the solid lines, representing actual outputs, reach steady-states that overlie the dashed lines, representing corresponding desired outputs, illustrating the accuracy of the training procedure.

3.2.2 MATLAB ENUMERATION OF ADJUSTABLE TSC-STRENGTH CONFIGURATIONS

To determine the possible effects of chronic administration of drug/hormone combinations on a patient population, all of the configurations, starting from each of the 3 different, representative networks that could be generated by up to 6 adjustments at an increment of 0.50 (MS-model) or 1 (MSS-model) were analyzed. The number of adjustments was limited to 6 due to computational overhead (see B.20: Hardware Considerations). Instead of choosing one representantive parameter set for neuroadaptation experiments as with the M-model, this analysis was repeated for each drug or combination using all 3 networks of each of the MS- and MSS-models and the adapted monoamine levels of each was pooled for each model. While the M-model demonstrated the neuroadaptive pathways available to a single individual with chronic administration of an antidepressant or combination, the MS- and MSS-models demonstrate the compiled adaptive pathways available to 3 individuals. The distributions of monoamine and CORT levels over all of the networks that are adapted to spcific drug/hormone combinations are shown as histograms.

3.2.2.1 MS-MODEL SINGLE DRUG, DRUG COMBINATION, AND DRUG/HORMONE COMBINATION HISTOGRAM ANALYSES

A central goal of this study was to use the trained network models to evaluate the possibility that combinations of antidepressant drugs, or combinations of drugs and hormones, could be more therapeutically effective that single SSRIs. Configurations adapted to chronic administration of select drugs and hormones in combination with SSRI were analyzed. We use the term “SSRI” rather than “Escitalopram” in the MS- and MSS-model analyses because the MS- and MSS-models were trained on more than one SSRI (e.g., Citalopram, Escitalopram, Fluoxetine, etc.). The results of some specific drug and hormone combinations are shown in Figures 12 and 13. The rows of these 2 sets of histograms (Figures 12 and 13) show the monoamine and CORT distributions of all configurations starting from all 3 representative networks that were adapted to SSRI alone, to SSRI paired with another drug or hormone, and SSRI combined with the two other drugs or a drug and a hormone. Each column of these 2 sets of histograms (Figures 12 and 13) corresponds to a specific transmitter or hormone unit (5HT, NE, DA or CORT). Viewing the histograms down the columns shows how the distributions of monoamine and CORT levels are affected by the different drugs and combinations. In this histogram figure and in all subsequent histogram figures the baseline, average, and therapeutic levels of each transmitter or hormone will be represented with a blue,

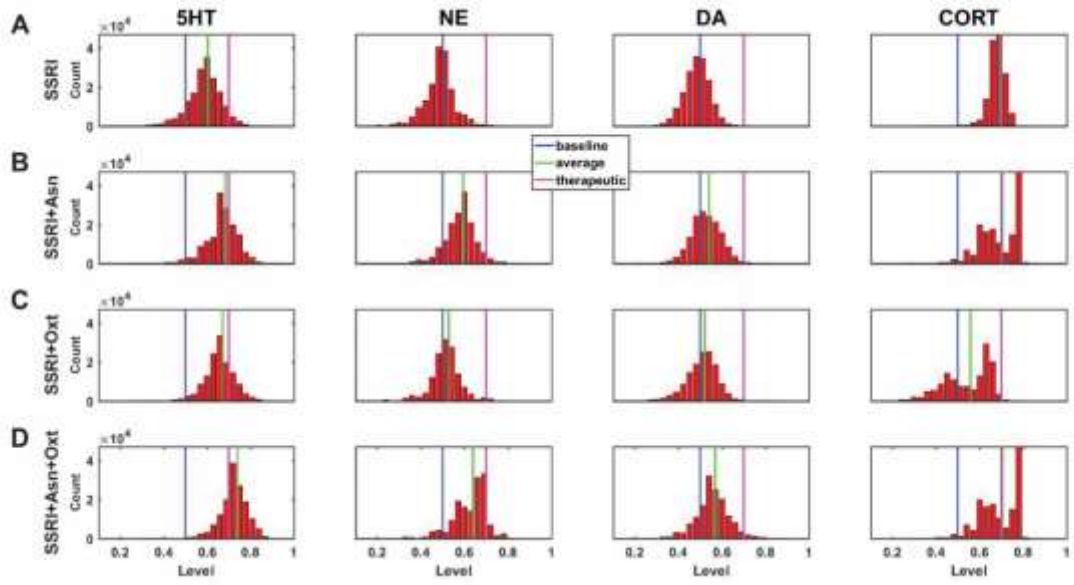


Figure 12: MS-model histograms showing number of adapted configurations expressing different monoamine and CORT levels with combinations of SSRI, Asenapine, and Oxytocin. Networks were adapted to SSRI alone (A), SSRI+Asenapine (Asn, an antipsychotic drug) (B), SSRI+Oxytocin (Oxt, a hormone) (C), and SSRI+Asn+Oxt (D). (B) and (C) show that combining an SSRI with either Asn or Oxt increases the proportion of high monoamine and low CORT states over the SSRI by itself. (D) shows that combining an SSRI with both Oxt and Asn further increases the proportion of high monoamine and low CORT states. These histograms suggest that combining an SSRI with either Oxt, Asn, or both may be therapeutic for a greater proportion of patients than an SSRI administered alone.

green, or magenta line, respectively. Although "therapeutic" monoamine levels have not been quantified, we set the therapeutic 5HT, NE, and DA floors and the therapeutic CORT ceiling to 0.70 using estimates based on experimental findings described in B.16: Setting Therapeutic Criteria.

Figure 12A shows the results of adaptation to SSRI alone, 12B shows SSRI paired with Asenapine (an antipsychotic drug), 12C shows SSRI paired with Oxytocin (a peptide neurohormone), and 12D shows SSRI combined with both Asenapine and Oxytocin. Figure 12B shows that combining SSRI with Asenapine not only increases the proportion of adapted states with therapeutically elevated (toward the right) 5HT, but also shifts the NE histogram to the right as well increasing the proportion of adapted states with elevated NE. Figure 12B also shows that the combination of SSRI and Asenapine can decrease CORT levels in a higher proportion of adapted configurations below the therapeutic ceiling (toward the left). In Figure 12C, the combination of an SSRI and Oxytocin also shifts the 5HT distribution to the right and increases

the proportion of adapted states with low CORT. The combination of all 3 factors (SSRI, Asenapine, and Oxytocin) in Figure 5D increases the proportion of adapted states with high monoamine levels for all 3 monoamines, and also increases the proportion of adapted states with low CORT beyond the levels observed with SSRI by itself.

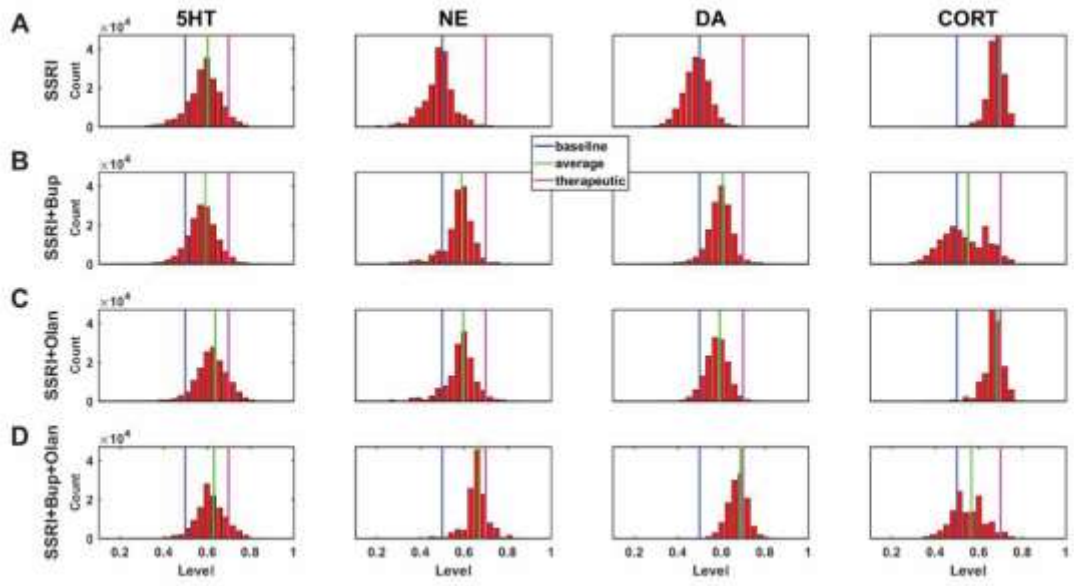


Figure 13: MS-model histograms showing number of adapted configurations expressing different monoamine and CORT levels with combinations of SSRI, Bupropion, and Olanzapine. Networks were adapted to SSRI alone (A), SSRI+Bupropion (Bup, a NET and DAT blocker) (B), SSRI+Olanzapine (Olan, an antipsychotic drug) (C), and SSRI+Bup+Olan (D). (B) and (C) show that combining an SSRI with either Bup or Olan increases the proportion of high monoamine and low CORT states over the SSRI by itself. (D) shows that combining an SSRI with both Bup and Olan further increases the proportion of high monoamine and low CORT states. The histograms in (D) illustrate that the combination of SSRI+Bup+Olan shifts the monoamine and CORT histograms, especially those of NE and DA, toward more therapeutic states, suggesting that this combination can be therapeutic for a greater proportion of patients than an SSRI administered alone.

Figure 13A shows the results of adaptation to SSRI alone, 13B shows SSRI paired with Bupropion (an atypical antidepressant), 13C shows SSRI paired with Olanzapine (an antipsychotic drug), and 13D shows SSRI combined with both Bupropion and Olanzapine. Figure 13B shows that adaptation to the combination of SSRI and Bupropion can increase the proportion of adapted states with high NE and DA levels over that observed with the SSRI by itself. It also shows that this combination decreases CORT levels in a higher proportion of adapted states than the SSRI by itself. Figure 13C shows that the combination of SSRI and Olanzapine can increase the proportion of adapted states with therapeutic 5HT over the SSRI by itself. The combination of all 3 (SSRI,

Bupropion, and Olanzapine) in Figure 13D was found to shift all 3 of the monoamine (5HT, NE and DA) histograms to the right (toward high monoamine levels) and increase the proportion of adapted states that reduce CORT below its therapeutic ceiling. Overall, these histograms illustrate how combinations of chronic drugs (or of drugs and hormones) can increase the proportion of adapted states with elevated monoamines and reduced CORT levels (see 4.5).

3.2.2.2 MSS-MODEL SINGLE DRUG, DRUG COMBINATION, AND DRUG/HORMONE COMBINATION HISTOGRAM ANALYSES

Each MSS-model histogram in Figures 14 and 15 shows the numbers of adjusted TSC-strength configurations adapted to each drug/hormone combination that had levels of 5HT, NE, DA, and CORT falling within discrete bins as indicated. Comparison of Figure 14A (SSRI alone) with 14B shows that combining SSRI with Quetiapine not only increases the proportion of adapted states with therapeutically elevated (toward the right) 5HT, NE, and DA, but also increases the proportion of adapted states with therapeutically decreased (toward the left) CORT. Figure 14C shows that combining an SSRI with Oxytocin increases the proportion of adapted states with therapeutically elevated 5HT and DA as well as the proportion of states with low CORT. Figure 14D shows that the combination of all 3 factors (SSRI, Quetiapine, and Oxytocin) also increases the proportion of adapted states with therapeutically elevated 5HT and DA and low CORT. Figure 14D also shows an interesting bi-modal distribution of NE, where one peak of adapted states is at or below baseline NE levels and the second peak is shifted to the right above the NE therapeutic floor.

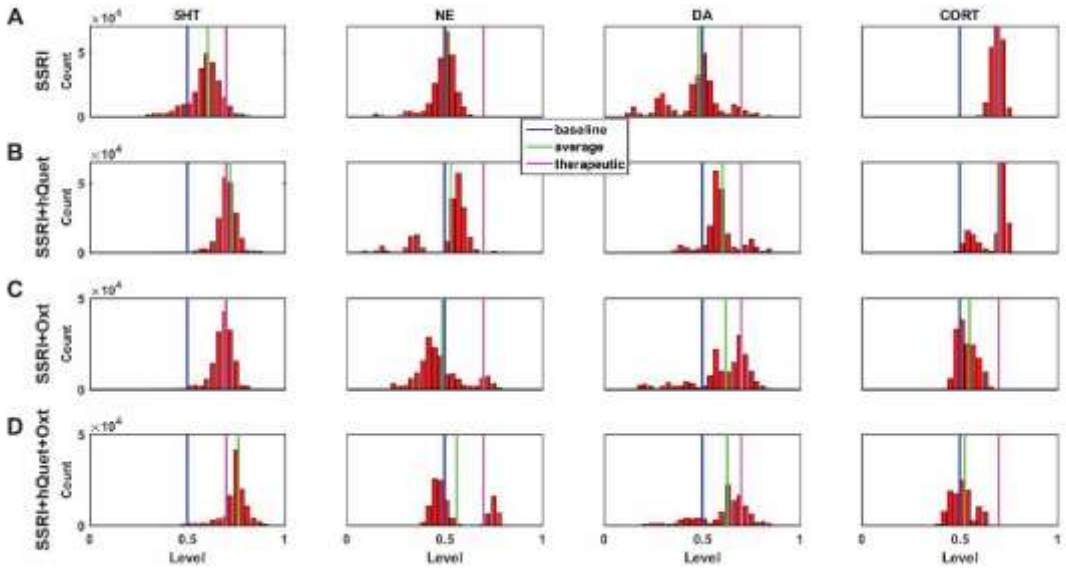


Figure 14: MSS-model histograms showing number of adapted configurations associated with different monoamine and cortisol levels with combinations of SSRI, Quetiapine, and Oxytocin. Networks were adapted to SSRI alone (A), SSRI+Quetiapine (hQuet, an antipsychotic drug) (B), SSRI+Oxytocin (Oxt, a hormone) (C), and SSRI+hQuet+Oxt (D). (B) and (C) show that combining an SSRI with either hQuet or Oxt increases the proportion of high monoamine and low CORT states over the SSRI by itself. (D) shows that combining an SSRI with both hQuet and Oxt further increases the proportion of high monoamine and low CORT states.

Comparison of Figure 15A and Figure 15B shows that combining SSRI with Asenapine increases the proportion of adapted states with therapeutically elevated levels of all 3 monoamines and low CORT. Figure 15C shows that combining an SSRI with TEST increases the proportion of adapted states with therapeutically high 5HT and DA and low CORT. Figure 15D shows that the combination of SSRI, Asenapine, and TEST further increases the proportion of adapted states with therapeutically elevated monoamines and low CORT, and shifts all 4 of these distributions further toward their respective therapeutic poles. These histograms illustrate how the MSS-model can be used to identify drug or drug and hormone combinations that could potentially be therapeutic for a higher proportion of male depressed patients than SSRIs by themselves (see Discussion).

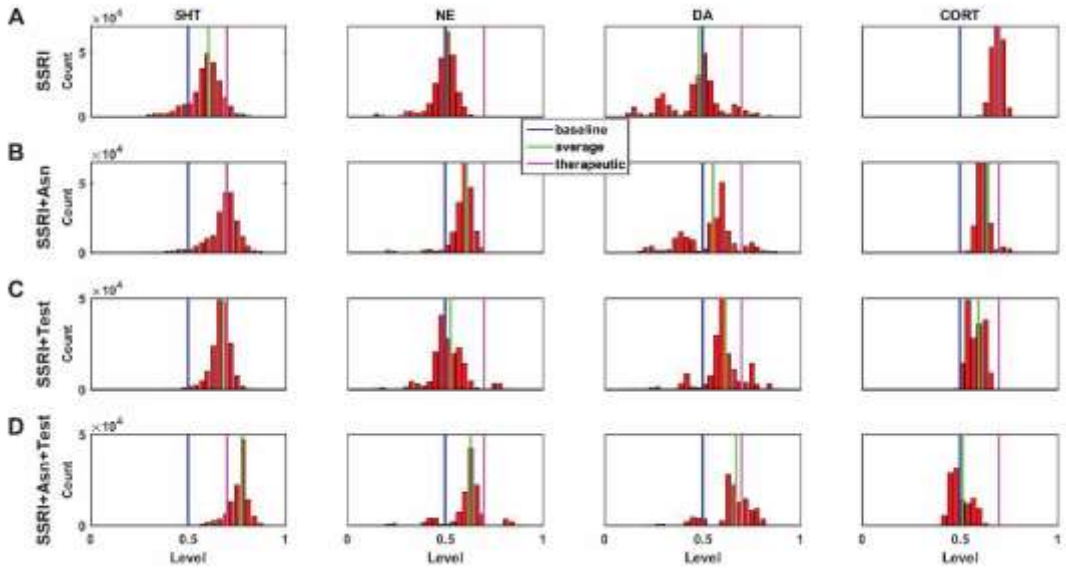


Figure 15: MSS-model histograms showing number of adapted configurations associated with different monoamine and cortisol levels with combinations of SSRI, Asenapine, and Testosterone. Networks were adapted to SSRI alone (A), SSRI+Asenapine (an antipsychotic drug) (B), SSRI+Testosterone (TEST, a hormone) (C), and SSRI+Asn+TEST (D). (B) and (C) show that combining an SSRI with either Asn or TEST increases the proportion of high monoamine and low CORT states over the SSRI administered alone. (D) shows that combining an SSRI with both Asn and TEST further increases the proportion of high monoamine and low CORT states.

3.2.3 PREDICTING THE EFFICACY OF DRUG AND HORMONE COMBINATIONS

3.2.3.1 MS-MODEL DRUG/HORMONE COMBINATION SCREEN

The monoamine levels for the 3 networks adapted to each of a set of clinically reasonable drug or hormone pairs and triples were compiled and the average monoamine levels were computed. The average levels of each of the 3 monoamines for each chronic drug or hormone combination are shown as rows in the heatmap in Figure 7. Each column represents the level of one monoamine (5HT, NE, or DA, moving across the columns). For purposes of illustration, quantification, and ordering, the 3 monoamine levels can be combined into a monoamine vector: [5HT NE DA]. Baseline, therapeutic, and excess monoamine reference vectors can then be defined. The baseline reference vector consists of the baseline monoamine levels [0.50 0.50 0.50], the therapeutic reference vector consists of the therapeutic monoamine levels [0.70 0.70 0.70], and the excess monoamine reference vector consists of excessively high monoamine levels [0.80 0.80 0.80]. The excess monoamine reference vector represents a tripling of the acute level and is

included in order to identify drug pairs and triples that may elevate the monoamines high enough to produce unwanted side effects (Shrier, Diaz et al. 2000, Boyer and Shannon 2005).

All adapted monoamine vectors [5HT NE DA] that had any monoamine elevated above 0.80 were ordered by their vector distance from the excess monoamine vector; all remaining adapted monoamine vectors were ordered by their vector distance from the therapeutic reference vector. This figure can be used as a tool to help predict monoamine levels following adaptation to chronic administration of each of the selected drug combinations, and to identify potentially effective interventions for the different subtypes of depression that are believed to respond to elevations in different monoamines (Malhi, Parker et al. 2002, Malhi, Parker et al. 2005)(see 4.5).

The MS-model was used to evaluate the configurations adapted to chronic administration of 60 drug or drug/hormone pairs and triples. The 27 pairs consisted of SSRI paired with each of the 27 drugs and hormones that were used as individual (single) inputs in model training. The 33 triples consisted of the subset of those pairs that have been used to augment SSRI action clinically (or experimentally in 1 case), combined with a third substance that was either Oxytocin (a hormone), Antalarmin (a CRF1 receptor antagonist), or Olanzapine (an antipsychotic). These 3 substances were selected due to recent preliminary evidence suggesting that Oxytocin, Antalarmin, and Olanzapine could potentially have antidepressant effects either by themselves or in combination with another antidepressant (Corya, Andersen et al. 2003, Ducottet, Griebel et al. 2003, Jutkiewicz, Wood et al. 2005, Parker, Buckmaster et al. 2005, Mathews, Garcia et al. 2006, Yoshida, Takayanagi et al. 2009). Figure 16 below shows the results of this analysis with the MS-model.

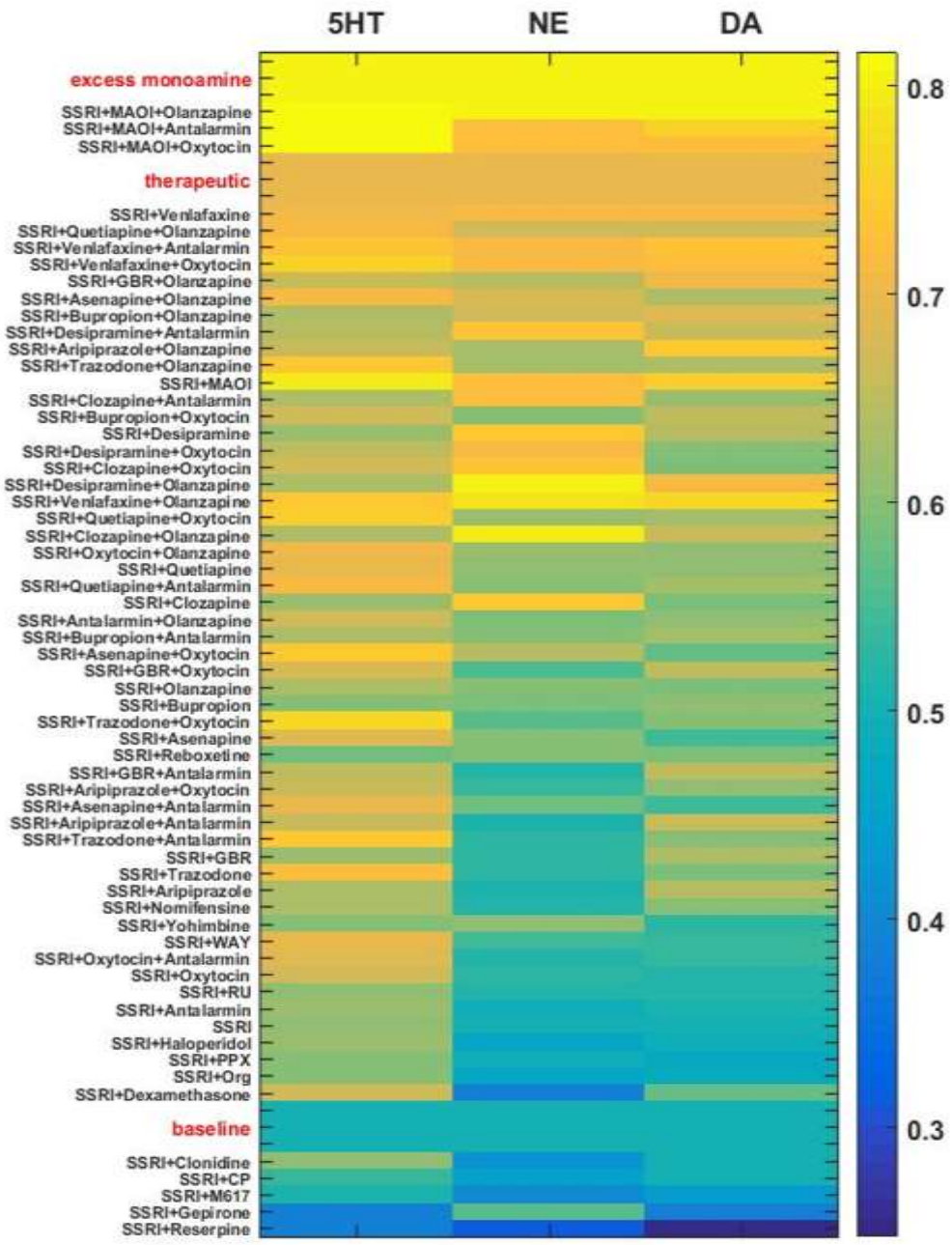


Figure 16: Heatmap of MS-model adapted monoamine levels with SSRI, all other drugs paired with SSRI, and selected 3-drug combinations. Adapted monoamine levels were averaged over the 3 networks and expressed as a vector [5HT NE DA]. The excess monoamine reference vector, representing levels high enough that they could be associated with unwanted side effects, was set to [0.80 0.80 0.80]. All drug combinations that resulted in 1 or more excess monoamine levels were ordered by vector distance from the excess monoamine reference vector. The therapeutic and the baseline reference vectors were set to [0.70 0.70 0.70] and [0.50 0.50 0.50], respectively. The baseline reference vector and all remaining drug pair and triple vectors were ordered by vector distance from the therapeutic reference vector. Abbreviations: GBR-12909, GBR; WAY-100635, WAY; Pramipexole, PPX; RU-28362, RU; Org-34850, Org; CP-96345, CP; Monoamine oxidase inhibitor, MAOI.

The MSS-model was used to evaluate networks adapted to chronic administration of SSRI, SSRI paired with 24 clinically relevant drugs or hormones, triples consisting of Testosterone and each of the 24 pairs, and triples consisting of Testosterone, Oxytocin, and one drug from each pair for a total of 74 drug/hormone combinations (plus SSRI by itself, for a total of 75 experiments). The results of this analysis can be viewed in Figure 17 below. The majority of the antidepressant combinations in Figure 17 show a reduction of NE levels (heatmap colors closer to the "blue" range) with chronic administration. It is unclear if the adapted configurations to these combinations all reduce NE, however. The histogram in Figure 14D illustrates that neuroadaptation to chronic antidepressant combinations (specifically SSRI/Quetiapine/Oxytocin in 14D) can lead to a bi-modal distribution of NE, wherein about half of the neuroadapted configurations result in reduced NE levels, and the remaining half of the neuroadapted configurations result in elevated NE levels. The combined results of Figure 14D and Figure 17 suggest that different depressed male patients may respond to chronic administration of antidepressant with different patterns of NE release.

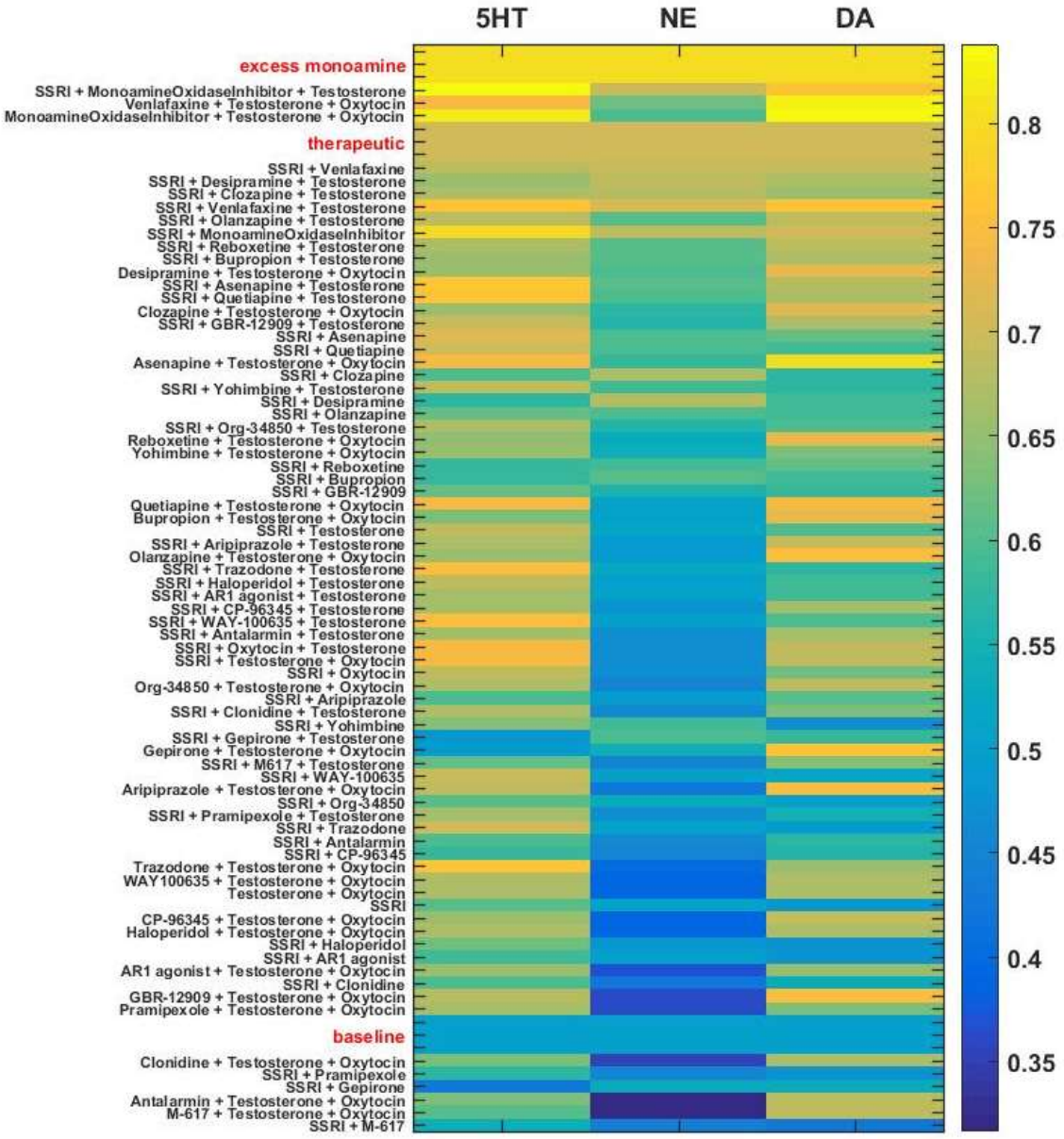


Figure 17: Heatmap of MSS-model adapted monoamine levels with SSRI, other selected drugs or hormones paired with SSRI, SSRI/other-drug/hormone triples, and drug/hormone/hormone triples. Adapted monoamine levels associated with neuroadaptation to SSRI, SSRI paired with other selected drugs or hormones, SSRI/other-drug/hormone triples, and drug (SSRI or other)/hormone/hormone triples were averaged over the three networks and expressed as a vector [$5HT_{avg}$ NE_{avg} DA_{avg}]. Vectors associated with drug or hormone pairs and triples, along with the baseline reference vector ([0.50 0.50 0.50]), were ordered by vector distance from the therapeutic reference vector ([0.70 0.70 0.70]). The exceptions were drug or hormone combinations that resulted in one or more excess monoamine levels (> 0.80), which were ordered by vector distance from the excess monoamine reference vector ([0.80 0.80 0.80]). These combinations produced monoamine levels high enough that toxicity could be of concern.

3.2.4 FULL-RANGE INDIVIDUAL-WEIGHT ADJUSTMENT (FRIWA) TO EVALUATE THE THERAPEUTICITY OF EACH ADJUSTABLE WEIGHT

Though we identified and examined adjustments in 10 (MS-model) or 13 (MSS-model) adjustable TSCs, it is possible that single TSCs can alone determine the therapeutic state in the MS- or MSS-model, regardless of the values of the weights representing the other adaptable TSCs. We define "therapeuticity" generally as the ability of a biological factor to alter the properties of a biological system in a therapeutic direction. Specifically here, therapeuticity is the ability of a TSC to alter 3 of the properties of interest in the MS- and MSS-models: the level of adaptation, the level of 5HT, and the level of CORT. Identification of the TSCs that could alone determine therapeutic state could enhance antidepressant drug design by identifying specific receptors or transporters that could be targeted in single-drug therapies.

In order to identify single adjustable TSCs that may be mediating therapeutic effects by themselves, a form of sensitivity analysis was conducted that evaluated the contribution of each individual adjustable TSC to therapeutic adaptation with chronic SSRI administration. Here we define "therapeutic configurations" as those adjusted TSC-strength configurations that endow their associated, adjusted network with 3 properties: adaptation (adaptation error lower than initial error (MS-model) or reduced by at least 25% of initial error (MSS-model); 5HT elevation (5HT >=0.70); and CORT reduction (CORT <=0.70)). The weights for each TSC were compiled for all resistant and all sensitive post-FRIWA configurations and averaged for each of the 3 representative networks separately in each model (see 2.2.2.2.3).

The average values of the TSC weights over either the resistant or sensitive configurations are plotted for each representative network in blue, red, or green for the MS- and MSS-models in Figure 18 and Figure 19, respectively. These figures illustrate that the average resistant and sensitive TSC strengths (corresponding to TSC network connection weights) differ between the 3 representative networks, but that the average resistant and sensitive TSC strengths are about the same in each network. Although the 3 networks are indeed different in their specific weight values, the FRIWA analysis shows that they are similar in that no single TSC in any of the 3 is determinative of the therapeutic state by itself. This finding is true of both the MS- and MSS-models.

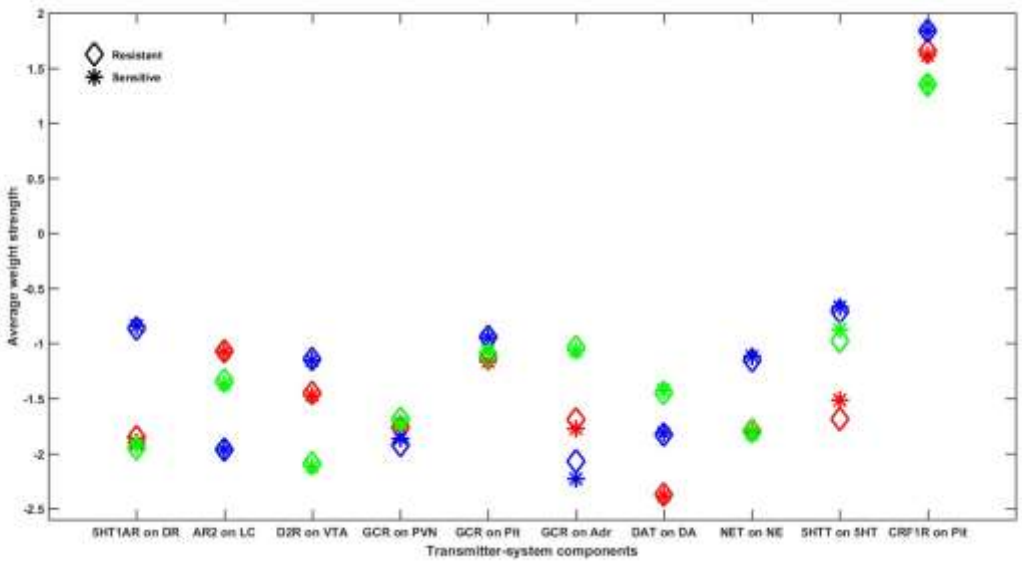


Figure 18: Comparison of MS-model average adjustable TSC strengths between resistant and sensitive configurations in all representative networks. Every configuration adapted to chronic SSRI that was also therapeutic (high 5HT and low CORT) at degree 6 was assessed for resistance to adjustments of each of the 10 adjustable TSCs. All TSC strength adjustments that resulted in configurations that were no longer adapted were excluded. Configurations that remained adapted and therapeutic following weight adjustments were determined to be "resistant" and adapted configurations that were no longer therapeutic following TSC adjustments were determined to be "sensitive." The average strength of each of the 10 adjustable TSCs in all of the configurations, excluding those in which that TSC itself was adjusted, was computed for both the resistant and sensitive configurations and plotted as asterisks or diamonds, respectively. The results for all 3 networks are represented on this single plot using 3 different colors (red, blue, or green) to distinguish between the mean adjustable TSC strengths of each network. Note that the average resistant and sensitive strengths for each adjustable TSC are very close in all 3 networks, illustrating that each individual TSC can provide a contribution to therapeutic resistance, but no single TSC by itself determines the therapeutic state.

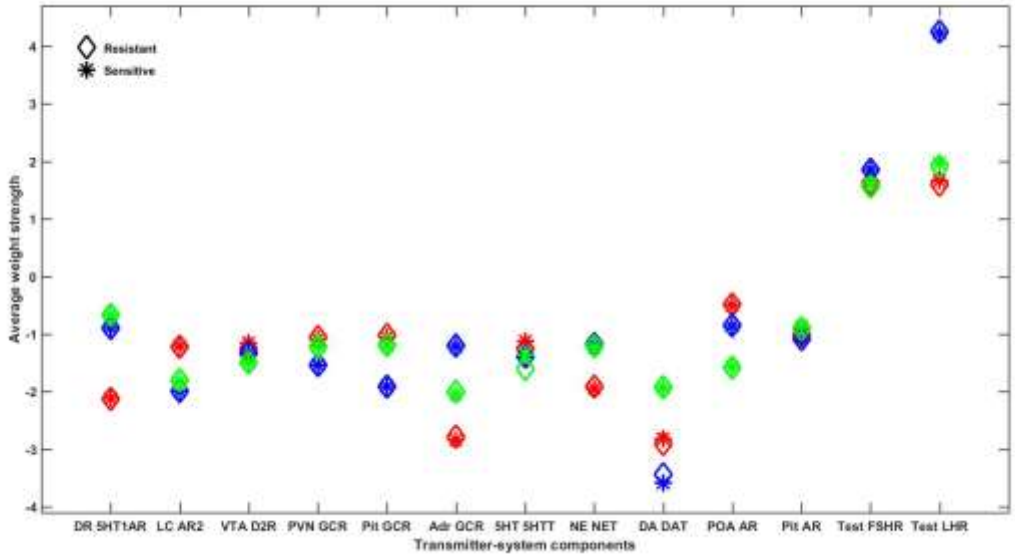


Figure 19: Average MSS-model adjustable TSC-strength comparison between resistant and sensitive configurations. Every therapeutic (high 5HT and low CORT) configuration adapted to chronic SSRI was assessed for resistance to full-range adjustments of the weights representing each of the 13 adjustable TSCs taken individually. The average strength of each of the 13 adjustable TSCs in all of the configurations, excluding those in which that TSC itself was adjusted using FRIWA analysis, was computed for both the resistant and sensitive configurations and plotted as asterisks or diamonds, respectively. The results for all 3 representative networks are shown on this single plot with 3 different colors (red, blue, or green) to distinguish between the mean adjustable-TSC strengths of each network. Note that the average resistant and sensitive strengths for each adjustable TSC are very close in all 3 networks, illustrating that no individual TSC mediates the therapeutic state by itself.

3.2.5 PAIRWISE CORRELATIONS BETWEEN ADAPTABLE TSC STRENGTHS

The FRIWA analysis considered 1 adjustable TSC at a time. It does not rule out the possibility that therapeuticity may be a property of correlations between pairs of TSCs rather than of single TSCs by themselves. To evaluate this possibility in both the MS- and MSS-models, pairwise correlations between all TSC weights over either all resistant or all sensitive configurations were computed for each representative network (separately in each model), but again, the TSC weights that were adjusted using FRIWA were removed because their values were manipulated. Even at the permissive significance level of $p = 0.05$, the analysis found no significant pairwise correlations between adjustable TSCs that were consistent over all 3 representative networks in either the resistant or the sensitive configurations. This finding was the same for both the MS- and MSS-models.

3.2.6 TEMPORAL-LOGIC MODEL-CHECKING

As described in 3.2.4, the FRIWA and correlation analyses examined a large space of configurations adapted to an SSRI and determined that no single TSC, nor pairs of TSCs, mediates therapeutic resistance by themselves in either the MS- or MSS-models. Neuroadaptation to chronic antidepressant, where each TSC change is incremental, can also be examined as a process to determine if specific states or degrees of neuroadaptation must be reached prior to arriving at therapeutic configurations. Linear temporal-logic (LTL) analysis can be used to elaborate all pathways of sequential TSC-strength adjustments in order to evaluate possible temporal relationships in neuroadaptation (see 2.3.2). This mode of analysis can be used to determine whether certain numbers of TSC-strength adjustments, once attained, will always lead to an adapted and therapeutic state.

The antecedent of the LTL propositions we analyzed specified that a specific TSC had been adjusted 3 times, either up or down (see 2.3.2 for details). The antecedent of 3 adjustments was chosen because it was halfway between 0 and 6, the total number of adjustments to which we were limited for technical reasons. The consequent queried whether all subsequent sequences of up to 3 adjustments in any subset of the 10 (MS-model) or 13 (MSS-model) TSCs would all lead to an adapted and therapeutic state (5HT >= 0.70 and CORT <= 0.70). Each LTL model-check was carried out using each of the 3 networks for 6 total adjustments in all TSCs, and only those model-checking results that were consistent over all 3 networks are reported for each model. All propositions returned false for both the MS- and MSS-models.

We next examined the more easily satisfiable propositions that once a specific TSC had been adjusted 3 times, either up or down, then all subsequent sequences of up to 3 adjustments in any subset of the adjustable TSCs would all lead to an adapted and therapeutic state, or the TSC no longer maintains its degree of adjustment. This proposition allowed for the possibility that failure to maintain an adapted and therapeutic state occurred because the specific TSC had not maintained the specified level of adjustment. All of these more satisfiable propositions, however, again returned false, as shown in Table 6 for the MS-model and Table 7 for the MSS-model.

Experiment	Condition (at 3 adjustments and beyond)	Leads to 5HT high and CORT low?
1	DR 5HT1AR desensitization	False
2	LC AR2 desensitization	False
3	VTA D2R desensitization	False
4	5HT 5HTT desensitization	False
5	NE NET desensitization	False
6	DA DAT desensitization	False
7	PVN GCR desensitization	False
8	Pituitary GCR desensitization	False
9	Adrenal GCR desensitization	False
10	Pituitary CRF1R desensitization	False
11	DR 5HT1AR sensitization	False
12	LC AR2 sensitization	False
13	VTA D2R sensitization	False
14	5HT 5HTT sensitization	False
15	NE NET sensitization	False
16	DA DAT sensitization	False
17	PVN GCR sensitization	False
18	Pituitary GCR sensitization	False
19	Adrenal GCR sensitization	False
20	Pituitary CRF1R sensitization	False

Table 6: Linear temporal-logic (LTL) analysis on the relationship between TSC-adjustments and a therapeutic state in the MS-model. Each LTL analysis was used to evaluate whether 3 steps of sensitization (adjustment up) or desensitization (adjustment down) of a specific TSC during neuroadaptation to chronic SSRI leads, over an ensuing 3 additional adjustments over any subset of the 10 TSCs, either to adapted and therapeutic configurations, or to failure to maintain sensitization or desensitization of the specific TSC. Only the results of LTL model-checks that were in agreement in all 3 networks are reported here. All propositions returned false, meaning that desensitization or sensitization of single adjustable-TSCs for 3 adjustment steps is not determinative of subsequent adapted and therapeutic states.

Experiment	Condition (at 3 adjustments and beyond)	Leads to 5HT high and CORT low?
1	DR 5HT1AR desensitization	False
2	LC AR2 desensitization	False
3	VTA D2R desensitization	False
4	5HT 5HTT desensitization	False
5	NE NET desensitization	False
6	DA DAT desensitization	False
7	PVN GCR desensitization	False
8	Corticotroph GCR desensitization	False
9	Adrenal gland GCR desensitization	False
10	POA AR desensitization	False
11	Gonadotroph AR desensitization	False
12	Testes FSHR desensitization	False
13	Testes LHR desensitization	False
14	DR 5HT1AR sensitization	False
15	LC AR2 sensitization	False
16	VTA D2R sensitization	False
17	5HT 5HTT sensitization	False
18	NE NET sensitization	False
19	DA DAT sensitization	False
20	PVN GCR sensitization	False
21	Corticotroph GCR sensitization	False
22	Adrenal gland GCR sensitization	False
23	POA AR sensitization	False
24	Gonadotroph AR sensitization	False
25	Testes FSHR sensitization	False
26	Testes LHR sensitization	False

Table 7: Linear temporal logic (LTL) analysis on the association between TSC-strength adjustments and the therapeutic state in the MSS-model. Each LTL analysis evaluated whether 3 steps of sensitization (adjustment up) or desensitization (adjustment down) of a specific adjustable TSC during neuroadaptation to chronic SSRI leads to adapted and therapeutic configurations when another 3 adjustments over all the TSCs are made. Only the results of LTL model-checking experiments that were in agreement in all 3 representative networks are reported. All propositions returned false, meaning that desensitization or sensitization of single TSCs for 3 adjustment steps does not lead to subsequent states that are all adapted and therapeutic.

The LTL analysis shows that 3 adjustments of any single adjustable TSC weight up or down will not guarantee that a therapeutic state will be reached. All propositions returned false to degree 6, and it is unlikely that they would be true if the LTL analysis extended to greater degrees of adjustment because that would entail additional opportunities for TSC de-adjustment and

overall de-adaptation. We did not attempt an exhaustive LTL analysis because the number of potentially relevant propositions that could be tested is simply too many. The result we generated, that 3 adjustments either up (sensitization) or down (desensitization) in no single TSC by itself can lead to states that are all therapeutic within 3 additional adjustments over the other TSCs or itself, supports the FRIWA analysis finding that adjustment of no single weight individually can determine the therapeutic state when the other TSCs can also adjust. These findings were in agreement between the MS- and MSS-models and impose potential challenges to effective antidepressant drug design (see 4.4).

We were next interested in whether there are connected regions (clusters) of therapeutic states in the space of TSC-strength configurations. The Henceforth LTL analysis represents a technological advancement exclusive to the MSS-model. This MSS-model analysis determined that there are few TSC-strength configurations (0.06% of therapeutic states over all three networks) where all configurations that both precede and leave that configuration (before and after an adjustment in a specific TSC) are therapeutic. However, there are clusters where most TSC-strength adjustments lead to therapeutic states; 37.8% of therapeutic states have the property that a majority of states within four adjustment steps are also therapeutic. This analysis shows that therapeutic states tend to be spatially localized in few pockets within the space of possible TSC-strength configurations. Overall these results suggest that the space of TSC-strength configurations has some structure, but also shows that there are no single, pairs, or subsets of TSCs that can guarantee therapeuticity by themselves.

CHAPTER 4: DISCUSSION

4.1 OVERVIEW

We have developed three computational models of the antidepressant response. The Monoamine-model (M-model) represents the monoaminergic and related transmitter systems, the Monoamine-Stress-model (MS-model) extends that to include the stress hormone system, and the Monoamine-Stress-Sex-model (MSS-model) extends the MS-model to also incorporate the interactions of the male sex steroids. All three models were trained to reproduce experimental data on acute inputs and used to examine neuroadaptation through transmitter system component (TSC) strength adjustments with chronic drug, hormone, or combinations. Analysis of all three models utilized both imperative and declarative programming methods and leveraged their complementary capabilities.

Our models differ in neurobiological detail (limited in M-model and expanded in MS- and MSS-models), structure (Region vs System), and training method (GA vs GD), but all three contribute to our understanding of adaptation to chronic antidepressant and suggest drug and drug/hormone combinations that are potentially more therapeutic than single antidepressants. Temporal-logic model-checking extended our use of declarative programming tools with analysis in the MS- and MSS-models of temporal relationships between different receptor-strength configurations in terms of neurotransmitter and hormone levels and receptor desensitization with adaptation to chronic SSRI. The three models differ substantially in extent, structure, and in method of parameter optimization, but all three are valid in that they accurately reproduce experimental observations over their domains and can therefore justifiably be used to make predictions in their respective domains. All three were used, specifically, to predict responses to chronic drug (or drug and hormone) combinations. Critically, all three models illustrate that heterogeneity in response to chronic antidepressant should be expected—due to the multiplicity in TSC types that are known to change their strength (expression and sensitivity) in that context.

4.2 COMPARISON WITH OTHER MODELS OF THE MONOAMINERGIC NERVOUS SYSTEM

Our models are the first of their kind in that they offer a more complete representation than all other available models of the monoaminergic neurotransmitter system and related interactions. They introduce declarative programming, exhaustive search methods, and temporal-logic model-checking to the neuropharmacology field.

A mathematical model of serotonin synthesis, release, and reuptake in axon terminals was developed by one group to better understand the effects of autoreceptor activation on DA and 5HT neuron firing patterns (Best, Nijhout et al. 2010, Best, Reed et al. 2010, Best, Nijhout et al. 2011). The same group used mathematical models of DR neurons with normal and low vesicular 5HT to study the adaptation of DR neurons to chronic SSRI. Through the use of differential equations that represent the concentrations and activity levels of different proteins involved in 5HT metabolism and release, the authors demonstrated that acute doses of SSRIs do not bring the burst firing of DR neurons back to normal, but chronic use of SSRIs do return the burst response to normative levels. Although many models of DA-producing neurons exist, one group notably produced a neuro-computational model of VTA afferents to better understand putative, neurobiological temporal-difference learning rules, designing an architecture that is similar to ours in that it includes multiple units representing non-monoaminergic neurons that interact with a unit representing a monoaminergic (specifically a VTA) neuron (Vitay and Hamker 2014).

Our models have features in common with these models, namely that they represent neuron activity levels and concentrations of transmitters. Our models can be distinguished from the others, however, in that they are the first of their kind to represent interactions between all three monoaminergic brain regions and regions producing non-monoaminergic transmitters. Among the potentially important factors left out of the M-model are presynaptic receptors, but they are included in the MS- and MSS-models. In the M-model, the non-monoaminergic transmitter units (tCRF, Tgal, and Tglu) are not included in the activation error calculation because they group together neurons from various brain regions that most likely do not all undergo drug-dependent changes of the same magnitude and direction. The non-monoaminergic units are differentiated into units representing discrete brain regions in the MS- and MSS- models.

We took the monoamine hypothesis as a starting point due to the finding that drugs that elevate the monoamines are more effective than placebo in treating depression without making the assumption that monoamines are deficient in depressed patients (Anderson 2000, Khan, Brodhead et al. 2005, Li, Li et al. 2014). We expanded this view by also considering the relationship between the monoamines and the HPA axis in the MS-model, and the relationship between the monoamines, HPA axis, and the male HPG axis in the MSS-model.

By modeling the monoaminergic neurotransmitter system, we do not exclude or refute other leading hypotheses on the neurobiology of depression. 5HT may or may not be deficient in

depressed patients, however, relief from depressive symptomology has been associated with elevated 5HT levels (Haddjeri, Blier et al. 1998, Evans, Golshan et al. 2002, Albert, Vahid-Ansari et al. 2014). Our approach does not assume that monoamine levels are deficient prior to antidepressant treatment, but it does assume that monoamine elevation, directly or indirectly, is involved in mediating antidepressant effects as consistent with the monoamine hypothesis (Schildkraut 1965, O'Reardon, Chopra et al. 2004).

One leading alternative to the monoamine hypothesis is that the decrease in the level of hippocampal brain-derived neurotrophic factor (BDNF) (involved in hippocampal neurogenesis) may lead to depression (Duman and Monteggia 2006). However, drugs that elevate monoamine levels also elevate hippocampal BDNF (Coppell, Pei et al. 2003, De Foubert, Carney et al. 2004, Sillaber, Panhuysen et al. 2008, Berger, Mehra et al. 2010). Other groups hypothesize that neuropeptide transmitter systems or the relative activations of interacting brain regions may be implicated in depressive symptomology (Mayberg, Liotti et al. 1999, Mayberg, Brannan et al. 2000, Kennedy, Evans et al. 2001, Holmes, Heilig et al. 2003, Flores-Burgess 2016). Depression relief associated with changes in the levels of neuropeptides or in the relative activity of brain regions, however, are also believed to be closely associated with elevations in monoamine levels (Mayberg, Liotti et al. 1999, Mayberg, Brannan et al. 2000, Lu, Barr et al. 2005, Rovin, Boss-Williams et al. 2012). Moreover, changes in TSC strength with chronic antidepressant administration will most likely cause changes in transmitter levels, and we assume that therapeutically elevated monoamines alleviate depressive symptomology through associations with mechanisms that have been suggested previously.

4.3 NEUROADAPTATION AS AN EXPLANATION FOR ANTIDEPRESSANT RESPONSE HETEROGENEITY

A key contribution of our study is a possible explanation for the clinical finding that antidepressants are effective in less than half of depressed patients (Rush, Trivedi et al. 2006, Young, Kornstein et al. 2009, Li, Li et al. 2014). All three models show that states neuroadapted to chronic SSRI can have a distribution of many different adapted 5HT levels, and the MS- and MSS-models extend this finding by also showing that states neuroadapted to chronic SSRI can also have a distribution of many different adapted CORT levels. These findings agree with the high variability in response and low efficacy rate for SSRIs that has been observed clinically (Rush, Trivedi et al. 2006, Young, Kornstein et al. 2009, Li, Li et al. 2014). All three models also show

that states neuroadapted to other chronic antidepressants also have distributions of many different monoamine levels. This is also consistent with the results of clinical trials using various chronic antidepressants (Rush, Trivedi et al. 2006).

Previous studies have found significant differences in baseline performance and behavioral response to antidepressant administration between rodent strains, with substantial variability even within inbred rodent strains (Liu and Gershenfeld 2001, Lucki, Dalvi et al. 2001, Ripoll, David et al. 2003, Petit-Demouliere, Chenu et al. 2005, Crowley, Brodkin et al. 2006). Differences in the phenotypic expression of the serotonin transporter have also been found within inbred rodent strains (Carneiro, Airey et al. 2009). Together, these findings support the prediction that different members of the same species can adapt differently to the same antidepressant.

Our models make the general prediction that the monoaminergic and neuroendocrine systems of individuals of the same species, especially if they differ genetically or in previous experience or in environmental conditions or in other relevant ways, should differ in the activity levels of neuroadapted brain regions and patterns of release of the three monoaminergic neurotransmitters (5HT, NE, and DA) and CORT under chronic administration of the same antidepressant drug or drug combination. Although genetic and environmental associations between monoamine levels, depression susceptibility, and antidepressant response have been explored (Rogers, Martin et al. 2004, Walf and Frye 2010), experiments designed directly to test this general prediction have not been undertaken but would be needed to validate our modeling approach. The null hypothesis is that the nervous systems of individuals of the same species will all attain the same patterns of neural region activity level and neurotransmitter and neurohormone release under chronic administration of the same antidepressant drug or drug combination, regardless of differences in strain or prior experience or environmental conditions or in other relevant factors. Verification of this null hypothesis would be of immense value in itself.

4.4 THERAPEUTIC NEUROADAPTATION TO CHRONIC ANTIDEPRESSANT AS OVERDETERMINED

The finding that only a subset of the many possible TSC-strength configurations is both adaptive and therapeutic raises the possibility that one, or only a few, of the adjustable TSCs are determinative of the therapeutic state. This possibility was evaluated with the MS- and MSS-models. First, we used FRIWA analysis (our customized variant of sensitivity analysis) to explore this possibility for individual TSCs in all 3 representative networks of each model. We found that

some configurations were “resistant” in that they remained adapted and therapeutic despite individual-weight adjustment (IWA) applied to a TSC. Other configurations were “sensitive” in that they did not remain adapted and therapeutic despite IWA applied to a TSC. The average values of individual TSC strengths, however, were essentially the same in resistant versus sensitive configurations (Figure 8) in all 3 networks of both (MS- and MSS-) models, indicating that no TSC by itself is determinative of the therapeutic state.

We then used correlation analysis to explore the possibility that pairs of TSCs were determinative of the therapeutic state, and considered all pairs that were significantly correlated at the relatively permissive significance level of $p = 0.05$. We found that no pair of TSCs was significantly correlated in either the resistant or sensitive configurations over all 3 representative networks (Figures 18 and 19), showing that no pairs of TSCs are together determinative of the therapeutic state in either the MS- or MSS- model.

We then used LTL analysis to explore the possibility that a specific TSC, once it reached a certain level of sensitization or desensitization, could guarantee a therapeutic outcome. For technical reasons (see B.20), the number of steps of adjustment we allowed in the strength of each TSC was limited to 6, and our LTL analysis took this constraint into account. For each TSC, we tested the truth or falsehood of two LTL propositions essentially asserting that if a given TSC has reached a certain level of sensitization or desensitization by three adjustment steps, then the network is guaranteed to arrive at an adapted and therapeutic configuration no matter what the other TSCs do in the remaining three adjustment steps. All of these propositions returned false in our LTL analysis (Tables 6 and 7). The MSS-model took this analysis a step further to include a novel LTL analysis designed to search for specific clusters of therapeutic states that are near each other in the space of TSC-strength configurations. It considered all degree-1 neighborhoods, defined as all the TSC-strength configurations within 1 adjustment step from a specified TSC-strength configuration. This LTL analysis found that there were no therapeutic TSC-strength configurations whose degree-1 neighbors were all also therapeutic. Clearly then, there would be no completely therapeutic neighborhoods of degree higher than 1.

What all of these analyses show is that no single TSC, nor pair of TSCs, nor TSCs that have attained a certain degree of adjustment, can determine the therapeutic state. They demonstrate, more generally, that the properties of interest in the model (the level of adaptation,

the levels of the 3 monoaminergic transmitters, and the level of CORT) are overdetermined by the 10 (MS-model) or 13 (MSS-model) TSCs.

In their overdeterminedness (or degeneracy), the MS- and MSS-models make contact with other models depicting phenomena at both network and neuronal levels of neurobiological organization. In the vertebrate brain, sensory signals, motor commands, and information in general is represented not by single neurons but by networks of neurons. These representations are overdetermined because the pieces of information are few relative to the number of neurons in the network that represents them. In consequence, the same information can be distributed in many different ways over a network, and neurons in the same network can vary greatly in their response properties in what has been termed a non-uniform distributed representation (Anastasio 1991, Anastasio 2010).

Overdetermination of physiological properties by the values of multiple, relevant parameters has also been demonstrated for single neurons and computational models of thereof (Edelman and Gally 2001, Golowasch, Goldman et al. 2002, Bucher, Prinz et al. 2005); reviewed in (Marder and Taylor 2011). The most well-known case in point was established by Eve Marder and colleagues in their model of the lateral pyloric neuron (LPN) in the lobster somatogastric ganglion (Taylor, Goaillard et al. 2009). In the invertebrate brain, information is sometimes represented not by neural networks but by single, very large (i.e. "giant") neurons that are identifiable from one animal to another. Experiments revealed that many different ion channels determine the electrophysiological properties of LPNs, and that the parameters that determine the function of ion channels of specific types can vary between LPNs from different decapods (Golowasch and Marder 1992, Golowasch, Goldman et al. 2002, Schulz, Goaillard et al. 2007).

The Marder group developed a biophysically detailed model of the LPN and identified 17 parameters (i.e. the conductances and some related properties of 10 ion channel types) that plausibly could vary between individual LPNs. They generated ~6 x 10^5 different configurations of these 17 parameters and found, after evaluating them all computationally, that 1304 of those configurations endowed the LPN model with the same, realistic set of electrophysiological properties (number of spikes, spike frequency, spike duration, burst duration, etc.). Rather than grouping into specific sets of values, however, the Marder team found that LPN models having equally realistic electrophysiological properties could vary greatly in the values of their 17 defining, ion-channel parameters (Taylor, Goaillard et al. 2009). By examining parameter value

distributions and correlations, they found further that no single parameter nor pair of parameters was determinative of LPN model properties.

Analogously, we find that many different configurations of TSC-strengths can endow the MS-model with the property of adaptation to simulated, chronic SSRI, but we take this a step further and show that the adapted configurations can also differ in other properties, namely in their levels of the monoamines. Overall, these computational studies suggest that there is a large amount of degeneracy in neurobiological systems in general. Our models specifically implicate overdeterminedness as a consequence of the complexity inherent in the antidepressant response that poses a challenge to the identification of an antidepressant drug or hormone combination that is effective in all patients (Edelman and Gally 2001). An approach that recognizes different subtypes of depression, and matches those with monoamine profiles predicted from computational models of the adapted antidepressant response, could provide an effective means of identifying promising drug combinations.

4.5 CLINICAL RELEVANCE OF THE MODELING RESULTS ON ANTIDEPRESSANT AND HORMONE COMBINATIONS

A consensus is forming around the general idea that multifactorial diseases should be treated with multidrug therapies (Stewart, McGrath et al. 2014, Perry, Sperling et al. 2015, Anastasio 2017). It has become common practice to treat psychiatric disorders with combinations of drugs, but the approach has been *ad hoc* and based mainly on clinical trial-and-error (Barowsky and Schwartz 2006). SSRI non-responders are often treated with combinations of two drugs (Trivedi, Fava et al. 2006), but systematic evaluation of the relative benefits of different combinations of two or more drugs in depression treatment has not occurred. Clinicians designing antidepressant augmentation strategies are challenged by the overwhelming complexity of depression neurobiology, and the potentially even more overwhelming number of possible drug combinations to choose from to treat depression.

The identification of novel, multidrug treatments for depression could proceed either through rational design or brute-force screening of drug combinations. The main challenge associated with rational design is the overwhelming complexity of the neurobiology of depression, which makes it extremely difficult to know *a priori* how any specific drug combination will work. The main challenge associated with brute-force screening is the sheer number of possible drug combinations, which grows geometrically with the number of drugs.

Our computational modeling approach addresses both challenges. It addresses rational design by computationally representing many aspects of the structure and function of the monoaminergic transmitter and stress hormone systems, whose interactions are central in depression neurobiology. It addresses combinatorial explosion by providing the means computationally to screen a large set of drug combinations, and to identify the most promising combinations for clinical evaluation. Addressing these dual challenges is crucial, because treatment with SSRI alone, which is currently the first-line treatment for depression, is less than 40% effective, and efficacy is not greatly increased when SSRI is combined with another drug (Rush, Trivedi et al. 2006).

The M-model predicted that the combination of an SSRI with SCH could potentially be therapeutic for a higher proportion of patients than SSRIs by themselves (see 3.1.6). It was also used to screen for the effects of combinations of antidepressants on the proportions of adapted states with high monoamines (see D.1: Potential Clinical Relevance of M-model Results). The MS-model was then used to identify drug and hormone combinations that could potentially be more therapeutic than single drugs for patients suffering from specific subtypes of depression (see Figure 16). Because the therapeutic effects of chronic antidepressant use have been associated with elevations in monoamine levels and reductions in CORT levels, we were specifically interested in configurations that reproduced these experimentally and clinically observed changes (Ruhe, Khoenkhoen et al. 2015) (Ceglia, Acconcia et al. 2004).

The MS-model identifies Asenapine, Olanzapine, Bupropion, and Oxytocin as adjuncts to SSRI therapy that hold particular promise. Precedent for the use of these adjuncts has been established clinically. Physicians in practice frequently resort to the augmentation of SSRIs with antipsychotics such as Asenapine and Olanzapine in SSRI-monotherapy non-responders (Mathews, Garcia et al. 2006) (Bjorkholm, Franberg et al. 2015). The atypical antidepressant Bupropion has also been found to relieve depressive symptoms in SSRI non-responders and is widely used clinically, either by itself or in conjunction with SSRI (Maron, Eller et al. 2009) (Zisook, Rush et al. 2006). Intranasal administration of the hormone Oxytocin combined with chronic SSRI also can be more effective in treating depressed patients than SSRI by itself (Parker, Buckmaster et al. 2005).

Our computational drug/hormone combination screen can potentially fine-tune combined pharmacotherapy for depression, as different subtypes of depression have previously been shown

to respond best to elevations in the levels of the different monoamines (Malhi, Parker et al. 2002, Malhi, Parker et al. 2005). Specifically, patients with non-melancholic, melancholic, or psychotic depression have been observed to respond best to antidepressants that elevate 5HT, NE, or DA, respectively (Malhi, Parker et al. 2005) (Parker, Roy et al. 1992) (Malhi, Parker et al. 2002). Drug combinations that included Trazodone (an SNRI), Olanzapine (an antipsychotic), and GBR-12935 (a DAT antagonist) tended to raise 5HT, NE, and DA levels, respectively, in the MS-model.

The MSS-model is specific to the male neuroendocrine system. The histograms in Figure 15 and the heatmap in Figure 17 show that certain combinations of antidepressants and the hormone testosterone could be more effective than SSRI by itself as a treatment for depression in men. Preliminary clinical studies suggest that Testosterone supplementation can enhance the antidepressant response (Orengo, Fullerton et al. 2005, Miller, Perlis et al. 2009). The combinations that included an SSRI, another drug that targeted the monoamines, and Testosterone were in the upper range of the Figure 17 heatmap, close to the therapeutic reference vector. Of note, SSRI/Desipramine/Testosterone, SSRI/Clozapine/Testosterone, and SSRI/Venlafaxine/Testosterone were found by the MSS-model to elevate levels of all 3 monoamines, and may increase the proportion of male patients who experience depression relief.

Our overall modeling strategy is both rational and brute force. It is rational in that the models incorporate, both in their structure and function, many aspects of the known interactions between the monoamines and related transmitter and neuroendocrine systems. It is brute force in that it can be used to screen large numbers of drug combinations computationally, and to predict the distributions of monoamine levels that could be expected in a diverse patient population in which each individual can adapt to the chronic drug regimen in their own unique way. Our models can be used to explore neuroadaptive configurations and to propose drug/hormone combinations that could be therapeutic for a higher proportion of patients than single-drugs by themselves. They could also be used to direct antidepressant drug-design toward specific depressive subtypes, by predicting the average levels of each of the three monoamines that would be expected in a patient population following adaptation to chronic administration of various drug combinations.

4.6 CALL FOR MORE DEPRESSION RESEARCH IN FEMALE MODELS

Unfortunately, data on the female neuroendocrine system sufficient to develop a female version of the MSS-model analogous to the male version was unavailable. Although the depression

literature has a reasonable volume of experimental data on the female sex-steroid system and depression, scientific reports of findings on the interactions between the monoaminergic-neurotransmitter, stress-hormone, and sex-hormone systems of females are rare. This lack of data from female animal models of depression is especially problematic because women are twice as likely as men to suffer from depression (Weissman, Bland et al. 1996) (Strine, Mokdad et al. 2008). Current clinical approaches to antidepressant pharmacotherapy are largely similar for both sexes (MacQueen, Santaguida et al. 2017), yet it has been observed that women and men respond better to different antidepressant drugs and combinations (Young, Kornstein et al. 2009).

Sex-specific computational models would provide the capability to individualize antidepressant treatment regimens by computationally screening for drug and drug and hormone combinations in models that incorporate sex differences in their structure and behavior. It is therefore crucial for experimental neurobiologists to collect data on female monoaminergic-hormonal interactions, in order to permit modelization of the female neuroendocrine system and computational identification of novel drug/hormone combinations that potentially could treat depressed women more effectively.

APPENDIX A: INTRODUCTION APPENDICES

A.1 OVERVIEW OF STRESS, HPA AXIS, AND CORTISOL

Stress is a condition that perturbs the physiological and psychological balance of an individual. The brain responds to stress through activation of the hypothalamic-pituitary-adrenal axis (HPA axis) (Pariante and Lightman 2008). Hypothalamic neurons located in the paraventricular nucleus (PVN) of the hypothalamus respond by releasing corticotropin-releasing factor (CRF), which in turn stimulates the release of adrenocorticotropin (ACTH) from the anterior pituitary gland, signaling the release of cortisol from the adrenal gland (Nemeroff and Vale 2005). In addition to its role in the stress response, CRF has been found to be involved in the regulation of several autonomic nervous system functions, including learning, memory, feeding, and reproduction (Valentino and Foote 1988, Chatterton 1990, Valentino, Foote et al. 1993, Petraglia, Florio et al. 1994). CRF is widely expression throughout the central nervous system and has even been found to be expression in some peripheral tissues (Waters, Rivalan et al. 2015).

CRF binding to CRF receptors in the anterior pituitary leads to the release of ACTH into the systemic circulation. ACTH binds to melanocortin type 2 (MCR-2) receptors of the adrenal gland, leading to secretion of cortisol and other steroid hormones, including androgenic steroids (Mountjoy, Robbins et al. 1992). Cortisol secretion has profound effects on metabolism and behavior through interactions with glucocorticoid receptors (GRs). GRs are widely distributed throughout the brain and peripheral tissues (Patel, Lopez et al. 2000). They are involved in mediating metabolic, cardiovascular, immune, and behavioral responses to stress (Evans, Murray et al. 2000, Furay, Bruestle et al. 2008, Matthews, Berry et al. 2015). Some of cortisol's known effects on the brain include regulation of neuronal survival, neurogenesis, hippocampus size, and the acquisition of new memories (Herbert, Goodyer et al. 2006, Pariante and Lightman 2008). Importantly, they are also involved in feedback inhibition of the HPA axis (Nestler, Barrot et al. 2002). Although they have been thought traditionally to mediate their negative feedback through a delayed feedback system involving intracellular GRs and genomic changes, there is recent evidence that GRs can also mediate a fast, nongenomic feedback effect as well through plasma-membrane receptors (Losel and Wehling 2003). This "fast feedback" effect mediated by GRs is not yet fully understood. GRs have been found to mediate negative feedback at all levels of the HPA axis (PVN, pituitary gland, and adrenal gland), and have also been found to mediate feedback inhibition on the HPA axis at the level of the hippocampus (Pariante and Lightman 2008).

Due to its involvement in mediating the physiological response to stress, dysregulation of the HPA axis has been studied extensively in the context of psychiatric disorders. Abnormalities in HPA axis regulation have been consistently found in association with depression (Gold and Chrousos 2002, Gillespie and Nemeroff 2005, Becker, Zeau et al. 2008). Evidence supporting the claim that HPA activity is dysregulated in depressed patients is supported by the outcome of the Dexamethasone test in humans. Dexamethasone is a synthetic glucocorticoid that induces a potent inhibitory effect on the HPA axis in healthy patients by stimulating the GRs that mediate HPA axis negative feedback. However, depressed patients do not respond to Dexamethasone, as evidenced by elevated cortisol levels in response to the test when compared to controls. Interestingly, antidepressant drugs that target the monoamines have been found to reverse this impairment in HPA axis negative feedback.

Evidence suggests that stressful life events are involved in the precipitation of depression (Shea, Walsh et al. 2005, Bravo, Dinan et al. 2014, Weder, Zhang et al. 2014). Activation of the stress response by acute stressors can be adaptive in the short-term (Korte, Koolhaas et al. 2005). However, chronic or repeated stress can prevent a return to a healthy state in susceptible individuals, and lead to the HPA axis hyperactivation observed in depressed patients (Heim, Newport et al. 2001, de Kloet, Joels et al. 2005). This hyperactivation is characterized by increased levels of cortisol in the saliva, plasma and urine, and increased size (as well as activity) of the pituitary and adrenal glands (Shea, Walsh et al. 2005).

Current antidepressant drugs target the monoaminergic neurotransmitter systems (Berton and Nestler 2006, Hamon and Blier 2013). In addition to (or potentially as an indirect result of) their influence on the monoamines, antidepressant drugs can reverse the hyperactivation of the HPA axis observed in depressed patients (Aihara, Ida et al. 2007). The relationships between the monoaminergic neurotransmitter-producing regions and the HPA axis regions are unclear. Both 5HT and NE have been shown to increase the secretion of CRF from the PVN, and CRF has been found to bind to CRF receptors in the DR, LC, and VTA to increase the activity level of these regions (Merchenthaler 1984, Valentino, Foote et al. 1993, Itoi, Suda et al. 1994, Stout, Owens et al. 2002, Reyes, Valentino et al. 2005, Heisler, Pronchuk et al. 2007, Reyes, Valentino et al. 2008, Wanat, Hopf et al. 2008, Sparta, Hopf et al. 2013). Interestingly, cortisol has been found to influence monoamine neurotransmission through transcriptional effects on proteins that regulate monoamine levels. Although cortisol binding to GRs in the DR has been found to increase the

activity of tyrosine hydroxylase hydroxylase (TH, an enzyme involved in the synthesis of NE and DA), desensitize 5HT1A receptors, and decrease the expression of 5HT transporters, it has also been found to increase expression of monoamine oxidase A, an enzyme involved in the breakdown of the monoamines (Caspi, Sugden et al. 2003, Clark, Pai et al. 2005, Lindley, She et al. 2005, Manoli, Le et al. 2005, Heydendael and Jacobson 2009, Miller, Wankerl et al. 2013, Bravo, Dinan et al. 2014). These effects seem to be opposing one another and are not completely understood.

These findings suggest that the relationship between the HPA axis and the monoamines involves many complicated interactions that are not clear-cut or simple to interpret. It is unclear whether monoamine elevation as a result of chronic antidepressant administration is responsible for normalizing cortisol levels, or vice versa. Our computational modeling experiments explore the relationship between drugs that target the monoaminergic neurotransmitter systems, the HPA axis, and cortisol.

A.2 OVERVIEW OF THE HPG AXIS AND DEPRESSION

Hypothalamus-Pituitary-Gonad (HPG) axis activity begins with hypothalamic secretion of gonadotropin-releasing hormone (GnRH), which leads to release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the pituitary gland (Moore and Price 1932, Harris 1964). LH and FSH then stimulate the gonads (ovaries and testes in females and males, respectively) to produce the gonadal hormones, estrogen (E), progesterone (P), and testosterone (T) (de Kretser, Hedger et al. 2002). The levels of each of these hormones are regulated by complex feedback. The cyclical nature of the HPG axis in females is dependent on folliculogenesis (Knight and Glister 2001). Serum concentrations of E and P rise and fall during pregnancy and puberty depending on the phase of each (Shang, Zhao et al. 2003). HPG hormone levels are dependent upon the reproductive state of the organism throughout life.

Depressive symptomology associated with menopause and andropause is believed to be related to a decline in the levels of the gonadal hormones (Buchanan, Eccles et al. 1992). Menopause and andropause are characterized by a loss of gonadal function resulting in dysregulation of the HPG axis (Rosario, Chang et al. 2004). Depressive symptomology has been observed to be associated with decreases in serum estrogen concentrations, and elevated levels of estrogen have been found to be associated with a more positive mood (Buchanan, Eccles et al. 1992). In adult women, reduced estrogen levels have even been considered to be a risk factor for depression (Steiner, Dunn et al. 2003). Hypofunction of the HPG axis in males, leading to

decreased testosterone levels, has also been shown to lead to depressive symptomology. The decline in sex steroid production by the gonads following menopause and andropause leads to a loss of hypothalamic feedback inhibition which actually stimulates GnRH and gonadotropin production (Schwall, Szonyi et al. 1988).

The sex steroids have been shown to interact with important proteins involved in the synthesis, actions, and breakdown of the monoamines. Ovariectomy has been found to decrease the expression of 5HT1A and 5HT2A receptors in the brain, which can be reversed through estrogen replacement (Joffe and Cohen 1998). When estrogen was administered to female rodents, an increase in the level of tryptophan hydroxylase-2 (TPH2, an enzyme involved in 5HT synthesis) was observed in DR neurons (Solomon and Herman 2009). Interestingly, monoamine oxidase levels have been found to decrease with estrogen but increase with progesterone in rodent studies (Frackiewicz, Sramek et al. 2000). TPH2 levels in the DR and 5HT2A receptor levels in the cortex have both been shown to increase with estrogen (Summer and Fink 1995, Donner and Handa 2009).

The effects of the sex steroids on mood are complex and involve interactions between many systems. It is likely that sex differences and cyclical changes in their levels play an important role on how these hormones affect mood. Computational modeling of the complicated interactions between the HPG axis, the HPA axis, and the monoaminergic neurotransmitters could help with our understanding of the relationship between the sex hormones and depression.

A.3 DIFFERENCE BETWEEN IMPERATIVE AND DECLARATIVE PROGRAMMING

Imperative and declarative programming languages are fundamentally different and provide complementary functionality. Specifically, imperative languages are designed for writing programs that compute efficiently along a single processing stream while declarative languages are designed for writing programs that can be used to evaluate the consequences of processing along many different streams. Imperative and declarative programs differ mainly in the nature of their statements.

A statement in an imperative language is a command (e.g., add two and two to get four) that is meant to be executed at a pre-specified point relative to the execution of other commands. This means that the order of the statements in the program determines the order of the execution of the statements. A statement in a declarative language is a declaration of a fact (e.g., two and two can be combined to get four) that may be executed as a command at various points relative to the

execution of other declarations. A declarative program can be written so that certain declarations execute in all possible orders, thereby elaborating the entire space of possible consequences of executions of those declarations. In the exhaustive Maude searches used in analysis of the M-model, the declarations that specified TSC-strength adjustments were allowed to execute in all possible orders. In this way, Maude evaluated the consequences for unit activations and monoaminergic transmitter levels of every possible combination of TSC strengths (TSC-strength configurations) that were reachable given the allowed number of adjustments. Temporal-logic model-checking analysis of the MS-model was carried out on samples of the state-space in order to reach states at deeper depths.

In this stochastic case, receptor-strength adjustment declarations did not execute in all possible orders, but only is some randomly chosen orders. The goal here was to characterize the properties of the receptor-adjustment process through analysis of a sufficiently large, random sample of the possible orders of declaration executions.

APPENDIX B: METHODS APPENDICES

B.1 DETAILS ON M-MODEL STRUCTURE AND FUNCTION

The monoaminergic units of the M-model have receptors for each transmitter type they receive from themselves and from other units. The specific receptors represented in the model are those that mediate the predominant effect of each transmitter as described in the literature. The monoaminergic regions, DR, LC, and VTA, have been found to project directly to one another (Beckstead, Domesick et al. 1979, Ornstein, Milon et al. 1987, Kalen, Skagerberg et al. 1988, Guiard, El Mansari et al. 2008). DR inhibits LC and VTA through 5HT2A and 5HT2C receptors (5HT2AR, 5HT2CR), respectively (Pessia, Jiang et al. 1994, Prisco, Pagannone et al. 1994, Stanford and Lacey 1996, Gobert, Rivet et al. 2000). DR also excites VTA through postsynaptic 5HT2ARs (Nocjar, Roth et al. 2002). LC and VTA excite DR through the noradrenergic receptor 1 (AR1) and D2 receptor (D2R), respectively (Svensson, Bunney et al. 1975, Baraban and Aghajanian 1980, Clement, Gemsa et al. 1992, Ferre and Artigas 1993, Martin-Ruiz, Ugedo et al. 2001). Evidence exists supporting the claim that LC and VTA inhibit one another (Aghajanian and Bunney 1977, Elam, Clark et al. 1986, Grenhoff, North et al. 1995), while some groups have found that these regions can excite each other (Deutch, Goldstein et al. 1986, Grenhoff, Nisell et al. 1993). Our model contains both excitatory and inhibitory receptors mediating the interactions between these regions. Their respective initial strengths are assigned during the parameter optimization process. DR and LC also secrete galanin onto one another (Melander, Hokfelt et al. 1986, Melander, Hokfelt et al. 1986, Xu, Zhang et al. 1998, Lu, Barr et al. 2005), which binds predominantly to inhibitory galanin receptors (galR1s) in these regions (Hawes and Picciotto 2004). There is some binding to excitatory galR2 receptors in the DR as well (Hawes and Picciotto 2004). The DR has inhibitory CRF1 and excitatory CRF2 receptors (CRF1R, CRF2R) mediating its responses to CRF innervations from the hypothalamus and the amygdala (Kirby, Freeman-Daniels et al. 2008, Spannuth, Hale et al. 2011, Wood, Zhang et al. 2013). The LC and VTA both have excitatory CRF1Rs mediating their responses to CRF released from the hypothalamus and the amygdala (Van Pett, Viau et al. 2000, Reyes, Valentino et al. 2008, Wanat, Hopf et al. 2008).

Each non-monoaminergic unit of the M-model represents all sources of its corresponding non-monoaminergic transmitter that impinge on the monoaminergic regions from other brain areas. Sources of CRF include amygdala and paraventricular nucleus CRF-producing neurons (Curtis, Bello et al. 2002, Hauger, Risbrough et al. 2006, Rodaros, Caruana et al. 2007). Widely

distributed in the central nervous system (CNS), sources of galanin include the LC, DR, and the hypothalamus, among others (Melander, Hokfelt et al. 1986). Sources of glutamate are also widely distributed, and include the cortex and the DR (Johnson 1994, Bagley and Moghaddam 1997, Tassone, Madeo et al. 2011, Shikanai, Yoshida et al. 2012, Liu, Zhou et al. 2014).

Together, the monoaminergic units in the M-model possess 23 total receptors (of 11 distinct receptor types) to represent their actions on themselves (via autoreceptors), their interactions with each other, and their responses to the non-monoaminergic transmitter units impinging on them. In addition to receptors (monoaminergic units) or generic weights (non-monoaminergic units), each unit also has a bias parameter representing intrinsic influence on its activity. The net input to any unit is then the sum of its inputs from other units, its input from itself, and its own intrinsic bias. For a monoaminergic unit of the M-model, which has a cognate receptor for each specific transmitter it receives, the amount of released transmitter is multiplied by the strength of the cognate receptor for that transmitter. The net input is the sum of all the receptor-times-transmitter products. For a non-monoaminergic unit of the M-model, which only has a generic weight for each connection it receives, the activation level of the sending unit is multiplied by the strength of the weight of its connection to the receiving unit. The net input is the sum of the weight-times-activation products (as in a conventional neural network). For any unit, monoaminergic or non-monoaminergic, its intrinsic bias is added to its net input from other units. The activation level of any unit is then computed according to the sigmoidal squashing function as $y = 1/(1+\exp(-x))$, where y is the activation level and x is the net input. As such, the activation levels of all units are bounded from 0 to 1.

On each time step, each unit updates its activation level by computing its net input and its resulting output according to the sigmoidal squashing function. Because the amount of released transmitter is equal to the activation level of the releasing unit, the squashing function ensures that no transmitter level falls below zero in the model. The monoaminergic transmitters are the exception, because their levels are reduced by their corresponding transporters by subtracting the numerical value representing the level of the transporter from the amount of released transmitter. Because this could cause the levels to fall below zero, the levels of the monoaminergic transmitters are actively bounded from below at zero (hard limit of zero). Any changes in TSC strength due to drugs are made prior to the unit updates, and any modifications in transmitter levels due to

transporters or drugs are made after the updates. The activation levels of all units are set to zero at time step zero, and the units then influence each other's activation for 150 time steps.

B.2 MS- AND MSS-MODEL CANONICAL WEIGHTS

B2.1 CANONICAL MS-MODEL WEIGHTS

The MS-model has 23 weights that were treated as "canonical weights." The canonical weights are the weights that mediate the known interactions of the monoaminergic nervous system and the stress-steroid system. The training procedure set the lower bound of the canonical weights to absolute value 1. Subsequent analysis revealed that the canonical weights developed the strongest weights and that each network was most sensitive to the canonical weights. They also revealed that the pruning procedure increased the sensitivity of the networks to the canonical weights.

Number	Weight	Polarity	References
1	DR to 5HT	+	(Hensler, Ferry et al. 1994, Monti 2010)
2	5HT to 5HT1AR	+	(Davidson and Stamford 1995, Blier, Pineyro et al. 1998)
3	5HT1AR to DR	−	(Davidson and Stamford 1995, Azmitia, Gannon et al. 1996)
4	5HTT to 5HT	−	(Lesch, Aulakh et al. 1993, Hensler, Ferry et al. 1994)
5	LC to NE	+	(Grenhoff, Nisell et al. 1993, Samuels and Szabadi 2008)
6	NE to AR2	+	(Cedarbaum and Aghajanian 1977, Washburn and Moises 1989)
7	AR2 to LC	−	(Cedarbaum and Aghajanian 1977, Washburn and Moises 1989)
8	NET to NE	−	(Iversen 2000, Bonisch and Bruss 2006)

9	VTA to DA	+	(Ornstein, Milon et al. 1987, Guiard, El Mansari et al. 2008)
10	DA to D2R	+	(Benoit-Marand, Borrelli et al. 2001, Perra, Clements et al. 2011)
11	D2R to VTA	−	(Hall, Sedvall et al. 1994, Perra, Clements et al. 2011, Koyama, Mori et al. 2014)
12	DAT to DA	−	(Ciliax, Heilman et al. 1995, Iversen 2000)
13	PVN to CRF	+	(Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984)
14	CRF to CRF1R	+	(Van Pett, Viau et al. 2000, Hauger, Risbrough et al. 2006, Holsboer and Ising 2008)
15	CRF1R to Pituitary Gland	+	(Van Pett, Viau et al. 2000, Nikodemova, Diehl et al. 2002)
16	Pituitary Gland to ACTH	+	(Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984)
17	ACTH to ACTHR	+	(Xia and Wikberg 1996, Papadimitriou and Priftis 2009)
18	ACTHR to Adrenal Gland	+	(Yang, Koistinaho et al. 1990, Xia and Wikberg 1996, Papadimitriou and Priftis 2009)
19	Adrenal Gland to CORT	+	(Grant, Forrest et al. 1957, Papadimitriou and Priftis 2009)
20	CORT to GCR	+	(Pariante and Miller 2001, Papadimitriou and Priftis 2009)
21	GCR to Adrenal Gland	−	(Loose, Do et al. 1980, Kalinyak, Dorin et al. 1987)

22	GCR to Pituitary Gland	−	(Morimoto, Morita et al. 1996, Ozawa, Ito et al. 1999)
23	GCR to PVN	−	(Morimoto, Morita et al. 1996, Ozawa, Ito et al. 1999)

B.2.2 CANONICAL MSS-MODEL WEIGHTS

The MSS-model has 36 weights classified as "canonical weights," because these weights mediate the known interactions of the monoaminergic nervous system, the stress-steroid system, and the sex-steroid system. The lower bound of the canonical weights was set to |1| during training. Upon further analysis it was determined that the canonical weights developed the strongest weights in the networks, and each network was most sensitive to changes in the canonical weights. The pruning procedure was also found to increase network sensitivity to the canonical weights.

Number	Weight	Polarity	References
1	DR to 5HT	+	(Hensler, Ferry et al. 1994, Monti 2010)
2	5HT to 5HT1AR	+	(Davidson and Stamford 1995, Blier, Pineyro et al. 1998)
3	5HT1AR to DR	−	(Davidson and Stamford 1995, Azmitia, Gannon et al. 1996)
4	5HTT to 5HT	−	(Lesch, Aulakh et al. 1993, Hensler, Ferry et al. 1994)
5	LC to NE	+	(Grenhoff, Nisell et al. 1993, Samuels and Szabadi 2008)
6	NE to AR2	+	(Cedarbaum and Aghajanian 1977, Washburn and Moises 1989)
7	AR2 to LC	−	(Cedarbaum and Aghajanian 1977, Washburn and Moises 1989)
8	NET to NE	−	(Iversen 2000, Bonisch and Bruss 2006)
9	VTA to DA	+	(Ornstein, Milon et al. 1987, Guiard, El Mansari et al. 2008)
10	DA to D2R	+	(Benoit-Marand, Borrelli et al. 2001, Perra, Clements et al. 2011)
11	D2R to VTA	−	(Hall, Sedvall et al. 1994, Perra, Clements et al. 2011, Koyama, Mori et al. 2014)
12	DAT to DA	−	(Ciliax, Heilman et al. 1995, Iversen 2000)
13	PVN to CRF	+	(Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984)
14	CRF to CRF1R	+	(Van Pett, Viau et al. 2000, Hauger, Risbrough et al. 2006, Holsboer and Ising 2008)

15	CRF1R to Corticotroph	+	(Van Pett, Viau et al. 2000, Nikodemova, Diehl et al. 2002)
16	Corticotroph to ACTH	+	(Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984)
17	ACTH to ACTHR	+	(Xia and Wikberg 1996, Papadimitriou and Priftis 2009)
18	ACTHR to Adrenal Gland	+	(Yang, Koistinaho et al. 1990, Xia and Wikberg 1996, Papadimitriou and Priftis 2009)
19	Adrenal Gland to CORT	+	(Grant, Forrest et al. 1957, Papadimitriou and Priftis 2009)
20	CORT to GCR	+	(Pariante and Miller 2001, Papadimitriou and Priftis 2009)
21	GCR to Adrenal Gland	–	(Loose, Do et al. 1980, Kalinyak, Dorin et al. 1987)
22	GCR to Corticotroph	–	(Morimoto, Morita et al. 1996, Ozawa, Ito et al. 1999)
23	GCR to PVN	–	(Morimoto, Morita et al. 1996, Ozawa, Ito et al. 1999)
24	POA to GnRH	+	(Pfaus, Jakob et al. 1994)
25	GnRH to GnRHR	+	(Kakar, Musgrove et al. 1992)
26	GnRHR to Gonadotroph	+	(Shacham, Harris et al. 2001)
27	Gonadotroph to FSH	+	(Shacham, Harris et al. 2001)
28	Gonadotroph to LH	+	(Shacham, Harris et al. 2001)
29	FSH to FSHR	+	(Dierich, Sairam et al. 1998)
30	LH to LHR	+	(Jia, Oikawa et al. 1991)
31	FSHR to Testes	+	(Catt, Baukal et al. 1979, Heckert and Griswold 1991)
32	LHR to Testes	+	(Belanger, Auclair et al. 1979, Catt, Baukal et al. 1979)
33	Testes to Testosterone	+	(Royland, Weber et al. 1994)
34	Testosterone to AR	+	(Grino, Griffin et al. 1990)
35	AR to POA	–	(Handa, Kerr et al. 1996)
36	AR to Gonadotroph	–	(Herbison, Skinner et al. 1996)

B.3 DETAILS ON MS-MODEL STRUCTURE AND FUNCTION

The structure matrix includes the subset of interactions between units in the model that are known from experimental observation. Inhibitory connections were given a −1, excitatory connections were given a +1, and connections of unknown polarity were given a 2 in the structure matrix. If the polarity was unknown by the literature, it was set by training algorithm.

SSRIs inhibit the 5HT transporter protein, so there is an inhibitory connection from SSRI to the 5HT transporter (Sanchez, Bergqvist et al. 2003, Nemeroff and Owens 2004). Nomifensine blocks the NE and DA transporters, and weakly blocks the 5HT transporter, so there are inhibitory connections from Nomifensine to NET, DAT, and 5HTT (Schacht and Heptner 1974, Brogden, Heel et al. 1979, Tatsumi, Groshan et al. 1997). Reboxetine potently blocks the NE transporter, so there is an inhibitory connection from Reboxetine to NET (Hajos, Fleishaker et al. 2004). Trazodone inhibits the 5HT transporter, is an agonist at the 5HT1A receptor, an antagonist of 5HT2A, 5HT2C, A1, and A2 receptors (Waldmeier 1982, Cusack, Nelson et al. 1994, Krege, Goepel et al. 2000 Asenapine is an agonist at 5HT1A receptors and an antagonist at 5HT2A, 5HT2C, A1, A2, D1, D2, D3, and D4 receptors {Ghanbari, 2009 #331, Balsara, Jadhav et al. 2005, Odagaki, Toyoshima et al. 2005, Corporation 2009, Shahid, Walker et al. 2009, Stahl 2009, Stahl 2009). Aripiprazole is an agonist at 5HT1A, 5HT2C, D2, D3, and D4 receptors, an antagonist at 5HT2A receptors, and interacts with A1, A2, B1, and B2 receptors with unknown polarity (Keck and McElroy 2003, Kroeze, Hufeisen et al. 2003, Shapiro, Renock et al. 2003). Bupropion inhibits the NE and DA transporters, so it has inhibitory projections to NET and DAT (Waldmeier 1982, Cooper, Wang et al. 1994, Stahl, Pradko et al. 2004). Humans metabolize Quetiapine to N-Desalkyl quetiapine (Nquet) so we simulated the effects of Quetiapine in the model by giving Quetiapine all the targets of both Quetiapine and Nquet (DeVane and Nemeroff 2001, Jensen, Rodriguiz et al. 2008). Quetiapine inhibits the NE transporter and 5HT2A, 5HT2C, A1, A2, D1, D2 and D3 receptors and is an agonist of 5HT1A receptors (DeVane and Nemeroff 2001, Jensen, Rodriguiz et al. 2008). Pramipexole (PPX) is an agonist at D2, D3 and D4 receptors (Mierau, Schneider et al. 1995). GBR is a DA transporter antagonist (TOCRIS , Andersen 1989). Clozapine is an agonist at 5HT1A receptors, is an antagonist at 5HT2A, 5HT2C, A1, D2, and D4 receptors, and has unknown polarity at A2, D1, and D3 receptors (Roth , Meltzer 1994, Newman-Tancredi, Chaput et al. 1996). Ketamine is an antagonist at NMDA receptors (Vollenweider and Kometer 2010). Reserpine depletes monoamines by inhibiting the activity of the vesicular monoamine

transporter 2 (VMAT2), which transports monoamines to the cell membrane for release into the extracellular space (Scherman and Henry 1984, Rudnick, Steiner-Mordoch et al. 1990). Because VMAT2 is not an element in our model, Reserpine sends inhibitory projections directly to 5HT, NE and DA. Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) with some antagonistic effects at the DA transporter (Roseboom and Kalin 2000, Wellington and Perry 2001). Desipramine is a tricyclic antidepressant that strongly inhibits the NE transporter and inhibits the 5HT and DA transporters with weaker affinity (Berti and Shore 1967). It is also an antagonist of the 5HT2A (Wander, Nelson et al. 1986). CP96345 (CP) is a neurokinin-1 receptor antagonist (Fong, Yu et al. 1992). Gepirone is an agonist of 5HT1A receptors (Blier and Ward 2003). RU28362 (RU) is a glucocorticoid receptor agonist (Sernia and Thomas 1994). Org34850 (Org) is a glucocorticoid receptor antagonist (Reynolds, Saunders et al. 2015). Oxytocin is a hormone input that projects to oxytocin receptors in the model (Gimpl and Fahrenholz 2001). Dexamethasone is a corticosteroid that acts as an agonist at glucocorticoid receptors but not mineralocorticoid receptors (Bamberger, Bamberger et al. 1995, Reul, Gesing et al. 2000, Pariante and Miller 2001). WAY100635 (WAY) is a selective 5HT1A receptor antagonist (Fletcher, Forster et al. 1996). Monoamine Oxidase Inhibitors (MAOI) block the activity of monoamine oxidase, which is an enzyme that mediates the breakdown of the monoamines (Stein 1960, Remick and Froese 1990). M617 is a galanin receptor 1 (galR1) agonist (Blackshear, Yamamoto et al. 2007). The CRF1R antagonist input has an inhibitory projection to the CRF1 receptor. Haloperidol is a dopamine D2 receptor antagonist (Schotte, Janssen et al. 1993). Olanzapine is dopamine D2 receptor antagonist and 5HT2A receptor antagonist (Pilowsky, Busatto et al. 1996). Clonidine is an alpha-2 receptor agonist (Unnerstall, Kopajtic et al. 1984). Yohimbine is an alpha-2 receptor antagonist (Perry and U'Prichard 1981). DR lesion, LC lesion, VTA lesion, PVN lesion, Amygdala lesion, Hippocampus lesion, PFC lesion and Adrenalecotmy are inhibitory to DR, LC, VTA, PVN, Amygdala, Hippocampus, PFC, the adrenal gland, respectively. The stress response begins with activation of the HPA axis, so the stress input sends an excitatory projection to the PVN (Sapolsky 2000, Gold and Chrousos 2002, de Kloet, Joels et al. 2005). Exogenous ACTH is excitatory to ACTH receptors (Kitay, Holub et al. 1959). Exogenous CRF is excitatory to CRF1 and CRF2 receptors (Merchenthaler 1984).

Each unit has a bias of unknown polarity.

Each region has an excitatory (+1) connection to the units it secretes. The DR secretes 5HT, glutamate, galanin, and NK1 (Melander, Hokfelt et al. 1986, Johnson 1994, Santarelli, Gobbi et al. 2001, Guiard, Guilloux et al. 2007, Soiza-Reilly and Commons 2011, Gagnon and Parent 2014, Liu, Zhou et al. 2014). The LC secretes NE, galanin, and NK1 (Holets, Hokfelt et al. 1988, Jordan, Kermadi et al. 1995, Pieribone, Xu et al. 1995, Maubach, Martin et al. 2002, Kawa, Barde et al. 2016). The VTA secretes DA and glutamate (Stuber, Hnasko et al. 2010, Root, Mejias-Aponte et al. 2014). The amygdala secretes glutamate, CRF, AVP, and NK1 (Buijs and Swaab 1979, Merchenthaler 1984, Curtis, Bello et al. 2002, Roberto, Schweitzer et al. 2004, Singewald, Chicchi et al. 2008). The PFC secretes glutamate (Bagley and Moghaddam 1997, Geisler, Derst et al. 2007, Albert, Vahid-Ansari et al. 2014). The PVN secretes CRF, AVP, oxytocin, and NK1 (Antoni, Fink et al. 1990, Yamashita, Kasai et al. 1991, Makara 1992, Emiliano, Cruz et al. 2007, Rodaros, Caruana et al. 2007, Bulbul, Babygirija et al. 2011, Feetham and Barrett-Jolley 2014). The hippocampus secretes glutamate (Bagley and Moghaddam 1997). The pituitary gland secretes ACTH and the adrenal gland produces cortisol (Kitay, Holub et al. 1959, Butler, Clarke et al. 1969, Seiden and Brodish 1971, Loose, Do et al. 1980).

Each enzyme or substrate has either an excitatory (+1) or inhibitory (−1) connection with its corresponding enzyme or substrate. The 5HT transporter is inhibitory on 5HT, the NE transporter is inhibitory on NE and DA, and the DA transporter is inhibitory on DA (Iversen 1971, Carboni, Tanda et al. 1990, Giros, Wang et al. 1994). In order to represent the 5HT synthesis pathway, there is an excitatory connection from tryptophan to tryptophan hydroxylase (TPH), an excitatory connection from TPH to 5-hydroxytryptamine (5HTP), 5HTP to 5HT-decarboxylase (5HTDC), from 5HTDC to 5HT, from 5HT to N-acetylserotonin O-methyltransferase (ASMT), and from ASMT to melatonin (Schott, Nicolai et al. 2010). Synthesis of NE and DA were represented with an excitatory connection from tyrosine to tyrosine hydroxylase (TH), an excitatory connection from TH to levadopa (L-DOPA), an excitatory connection from L-DOPA to aromatic L-amino acid decarboxylase (L-AADC), an excitatory connection from L-AADC to DA, an excitatory connection from DA to dopamine beta-hydroxylase (DBH), and an excitatory connection from DBH to NE (Cosentino, Marino et al. 2015). There is an inhibitory connection from monoamine oxidase (MAO) to 5HT, NE and DA to represent how MAO is responsible for the breakdown of the monoamines (Edmondson, Mattevi et al. 2004).

The neurotransmitters and hormones all have excitatory connections (+1) to their corresponding receptors to the model. 5HT projects to 5HT1A, 5HT1B, 5HT2A, and 5HT2C receptors. NE projects to A1, A2, B1, and B2 receptors. DA projects to D1, D2, D3, and D4 receptors. Glutamate projects to alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors. Galanin projects to galR1 and galR2. AVP projects to vasopressin receptor 1a (V1AR). CRF projects to CRF1 and CRF2 receptors. Cortisol projects to glucocorticoid (GC) and mineralocorticoid (MC) receptors. Oxytocin projects to oxytocin receptors. NK1 projects to NK1 receptors. ACTH projects to melanocortin 2 (MC2) receptors. GABA projects to GABA receptors.

Receptors have either excitatory (+1), inhibitory (−1), or unknown polarities on the brain regions and neurotransmitters. To account for the effect of presynaptic receptors, known presynaptic receptors had projections to neurotransmitters whose levels are regulated by the presynaptic receptor.

5HT1A receptors are inhibitory on DR, LC, PFC, and hippocampus neurons (Azmitia, Gannon et al. 1996, Blier, Pineyro et al. 1998, Celada, Puig et al. 2004, Santana, Bortolozzi et al. 2004, Puig, Artigas et al. 2005, Lanzenberger, Baldinger et al. 2013). 5HT1A receptors are also present on PVN neurons, but their overall polarity on PVN neurons has not been determined conclusively due to their presence on GABAergic interneurons impinging on PVN neurons (Pan and Gilbert 1992, Dinan 1996). Presynaptic 5HT1A receptors have been found to inhibit GABA release (Koyama, Matsumoto et al. 2002). 5HT2A receptors have been found to be inhibitory on LC but excitatory on the amygdala, PFC, and hippocampus (Haddjeri, de Montigny et al. 1997, Xu and Pandey 2000, Szabo and Blier 2002, Santana, Bortolozzi et al. 2004, Bombardi 2011). A1 receptors are excitatory on DR, amygdala, and PVN neurons (Baraban and Aghajanian 1980, Clement, Gemsa et al. 1992, Itoi, Suda et al. 1994, Cecchi, Khoshbouei et al. 2002). A2 receptors are inhibitory autoreceptors on LC neurons, and also reside with unknown polarities on VTA, amygdala, PFC, hippocampus, and PVN neurons (Cedarbaum and Aghajanian 1977, Talley, Rosin et al. 1996). AR2 receptors have also been found presynaptically to decrease NE, galanin, and NK1 levels (Cedarbaum and Aghajanian 1977, Kuraishi, Hirota et al. 1985, Tsuda, Yokoo et al. 1989, Bertolino, Vicini et al. 1997). B1 and B2 receptors are excitatory on LC, PFC and hippocampus neurons (Rainbow, Parsons et al. 1984). D1 receptors exist in the PFC with unknown polarity (Pirot, Godbout et al. 1992, Hall, Sedvall et al. 1994, Chen and Yang 2002). D2 receptors

are inhibitory autoreceptors on VTA neurons, are excitatory on amygdala, DR, and PFC neurons, and exist in the PVN with unknown polarity (Ferre and Artigas 1993, Hall, Sedvall et al. 1994, Haj-Dahmane 2001, Rosenkranz and Grace 2002, Brady and O'Donnell 2004, Succu, Sanna et al. 2007). D3 receptors are present in the PFC and PVN with unknown polarity (Levesque, Diaz et al. 1992, Succu, Sanna et al. 2007). D4 receptors are present in the PFC with unknown polarity (Primus, Thurkauf et al. 1997). AMPA and NMDA receptors have been found in the DR, LC, VTA, amygdala, PFC, and PVN, and vary in polarity depending on whether they are present on GABAergic interneurons or not, so their polarities were not fixed (Petralia and Wenthold 1992, Martin, Blackstone et al. 1993, Huntley, Vickers et al. 1994, de Kock, Cornelisse et al. 2006). galR1s are inhibitory galanin receptors, and they have been found to inhibit DR, LC, VTA, amygdala, and PVN neurons (Perez, Basile et al. 2002, Hawes and Picciotto 2004, Hawes, Brunzell et al. 2005). galR2s are excitatory on DR and hippocampus neurons (Hawes and Picciotto 2004, Elliott-Hunt, Pope et al. 2007). V1ARs have been found on amygdala and hippocampus neurons, and are excitatory on DR neurons and the pituitary gland (Ostrowski, Lolait et al. 1992, Rood and Beck 2014). CRF1 receptors are inhibitory on DR neurons, but are excitatory on LC, VTA, amygdala, PVN, and the pituitary gland (Van Pett, Viau et al. 2000, Kirby, Freeman-Daniels et al. 2008, Reyes, Valentino et al. 2008, Wanat, Hopf et al. 2008, Ji, Fu et al. 2013, Sparta, Hopf et al. 2013, Baiamonte, Valenza et al. 2014, Reyes, Bangasser et al. 2014). CRF2 receptors are excitatory on DR and VTA neurons (Wang, You et al. 2007, Spannuth, Hale et al. 2011, Wood, Zhang et al. 2013). GC receptors have been found on DR, LC, VTA, and hippocampus neurons with unknown polarity (Makara and Haller 2001, Makino, Smith et al. 2002, Lanfumey, Mongeau et al. 2008, Vincent and Jacobson 2014). They are inhibitory to PVN neurons, the pituitary gland, adrenal gland, and they decrease expression of the 5HT transporter (Fumagalli, Jones et al. 1996, Pariante and Lightman 2008, Heydendael and Jacobson 2010). They have been found to increase activity and/or expression of TPH, MAO, and TH (Clark, Pai et al. 2005, Lindley, She et al. 2005, Ou, Chen et al. 2006, Heydendael and Jacobson 2009). Mineralocorticoid receptors have been found in the hippocampus with unknown polarity (Herman, Watson et al. 1993, Patel, Lopez et al. 2000, Yau, Noble et al. 2001). They also mediate negative feedback on the HPA axis through inhibitory effects on the PVN, pituitary gland, and adrenal gland (Ratka, Sutanto et al. 1989, Patel, Lopez et al. 2000, Ladd, Huot et al. 2004). Oxytocin receptors have been found in the DR, LC, VTA, hippocampus, and pituitary gland with unknown polarity (Elands, Beetsma et al. 1988,

Breton, Pechoux et al. 1995, Gimpl and Fahrenholz 2001, Yoshida, Takayanagi et al. 2009). They are inhibitory in the amygdala (Buijs and Swaab 1979, Huber, Veinante et al. 2005). NK1 receptors are inhibitory on DR neurons, and have been found on LC, VTA, amygdala, PFC, and PVN neurons with unknown polarity (Tooney, Au et al. 2000, Conley, Cumberbatch et al. 2002, Rigby, O'Donnell et al. 2005, Renoldi and Invernizzi 2006, Gobbi, Cassano et al. 2007, Guiard, Guilloux et al. 2007, Haddjeri and Blier 2008, Feetham and Barrett-Jolley 2014). MC2 receptors are excitatory on the adrenal gland (Papadimitriou and Priftis 2009). GABA receptors have been found to be inhibitory on DR neurons, and have also been found on LC, VTA, amygdala, PFC, hippocampus, and PVN neurons, as well as the pituitary gland with unassigned polarities due to the presence of interneurons modulating their effects on the corresponding neurons (Baraban and Aghajanian 1980, Chang, Tran et al. 1980, Biggio, Corda et al. 1981, Roland and Sawchenko 1993, Van Bockstaele and Pickel 1995, Hatfield, Spanis et al. 1999, Cai, Flores-Hernandez et al. 2002, Katsurabayashi, Kubota et al. 2003, Puig, Santana et al. 2004, Tan, Zhong et al. 2004, Cornelisse, Van der Harst et al. 2007, Kreft and Zorec 2008, Bulbul, Babygirija et al. 2011, Jin, Bhandage et al. 2014, Kudo, Konno et al. 2014).

B.4 DETAILS ON MSS-MODEL STRUCTURE AND FUNCTION

The structure of the monoamine-stress-sex model (MSS-model) is based on known interactions within and between the monoaminergic neurotransmitter systems and the stress- and sex-hormone systems. The MSS-model is an extension of our previous monoamine-stress model (MS-model). Details on monoamine-stress interactions can be found in the Supplemental Material for our MS-model article (Camacho, Vijitbenjaronk et al. 2018). Details concerning monoamine-stress interactions with the sex-hormone system, which were used to augment the MS-model in creating the MSS-model, are described in this section.

All excitatory, inhibitory, or unknown polarities between structure connections are represented as a +1, −1, or +2 in the structure matrix. The polarities of connections where the polarity is unknown from the literature was assigned a polarity by the training procedure.

VTA DA neurons can co-release glutamate, GABA, and corticotropin-releasing factor (CRF), so there are excitatory projections from VTA to glutamate, GABA, and CRF.

The PVN secretes GnRH, so there is an excitatory connection from the PVN to GnRH (Moore and Price 1932). GnRH binds and activates the GnRH receptor (GnRHR), so there is an

excitatory connection from GnRH to GnRHR (Millar 2005). GnRHRs are excitatory on the pituitary gland, so there is an excitatory projection from GnRHR to the pituitary gland (Eidne, Sellar et al. 1992). The pituitary gland secretes the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Moore and Price 1932, Harris 1964). LH and FSH then bind to LH and FSH receptors on the gonads, so there are excitatory connections from LH to LH receptors (LHR) and FSH to FSH receptors (FSHR) (Simoni, Gromoll et al. 1997, Dufau 1998). LHR and FSHR activate the gonads, so there are excitatory projections from LHR and FSHR to the ovaries and testes (Whitelaw, Smyth et al. 1992, Simoni, Gromoll et al. 1997, Gunnarsson, Nordberg et al. 2003). The ovaries produce estrogen (E) and progesterone (P), and the testes produce testosterone (T) (de Kretser, Hedger et al. 2002). There are excitatory projections from the ovary to estrogen and progesterone and from the testes to testosterone.

ER-beta receptors increase TPH2 mRNA expression in rodents, so there is an excitatory projection from ER-beta to TPH (Donner and Handa 2009). Progesterone has also been found to increase TPH2 expression, so there is an excitatory connection from progesterone receptors to TPH (Bethea, Mirkes et al. 2000). Both estrogen and progesterone have been found to decrease MAO activity in female OVX Rhesus monkeys, so there are inhibitory projections from estrogen and progesterone receptors to MAO (Gundlah, Lu et al. 2002). Both estrogen and progesterone have also been found to decrease 5HT1A gene expression in female OVX Rhesus monkeys, so there are inhibitory projections from estrogen and progesterone receptors (ER and PR, respectively) to the 5HT1A receptor (Pecins-Thompson and Bethea 1999). Estrogen receptors exist in alpha and beta forms, described here as ER-alpha and ER-beta, respectively. A study using OVX female rats found that estrogen decreases 5HT1B receptor mRNA, so there is an inhibitory projection from estrogen receptors to 5HT1B receptors (Hiroi and Neumaier 2009). Estrogen administration to male rats has been found to increase 5HT2A receptor mRNA, so there is an excitatory projection from estrogen receptors to 5HT2A receptors (Summer and Fink 1995, Sumner and Fink 1998).

Estrogen has been found in OVX female rats to increase levels of tyrosine hydroxylase (TH) and dopamine beta-hydroxylase (DBH) mRNA through an unspecified estrogen receptor, so there are excitatory projections from both estrogen receptors to TH and DBH (Serova, Rivkin et al. 2002).

Testosterone administration to male rats has been found to increase 5HT2A receptor mRNA, so there is an excitatory projection from testosterone to 5HT2A receptors (Sumner and Fink 1998). Estrogen, progesterone, and testosterone receptors have been found in DR neurons and influence DR neuron firing with unknown polarity, so there are projections of unknown polarity from ER-alpha, ER-beta, PR, and AR to the DR (Alves, Weiland et al. 1998, Robichaud and Debonnel 2005).

Both ER-alpha and ER-beta receptors have been found to mediate the inhibitory effect of estrogen on hypothalamic neurons, so there are inhibitory projections from ER-alpha and ER-beta to the hypothalamus (Lagrange, Ronnekleiv et al. 1995, Roy, Angelini et al. 1999, Skynner, Sim et al. 1999, Herbison and Pape 2001). The inhibitory effect of progesterone on hypothalamic neurons are mediated by progesterone receptors, so there is an inhibitory projection from PR to the hypothalamus (Bashour and Wray 2012). ER-alpha mediates negative feedback on the HPG axis at the level of the hypothalamus, which is the receptor that is included as an inhibitory weight in the POA (Glidewell-Kenney, Hurley et al. 2007). The inhibitory effect of testosterone on hypothalamic neurons is mediated by androgen receptors, so there is an inhibitory projection from AR to the hypothalamus (Belsham, Evangelou et al. 1998).

Negative feedback on the HPG axis also occurs at the level of the Pituitary gland in both males and females, mediated by androgen receptors and ER-alpha receptors, respectively (Scully, Gleiberman et al. 1997, Thorner, Vance et al. 1998, Cheong, Porteous et al. 2014).

Androgen receptors, progesterone receptors, ER-alpha and ER-beta have all been found on both the ovary and testis (Due, Dieckmann et al. 1989, Vornberger, Prins et al. 1994, Brandenberger, Tee et al. 1998, Saunders, Fisher et al. 1998, Weil, Vendola et al. 1998, Makinen, Makela et al. 2001, Juengel, Heath et al. 2006). Testosterone provides negative feedback directly on the testis through activation of androgen receptors, so there is an inhibitory connection from the testosterone receptor to the testis (Darney and Ewing 1981). The polarity of the interaction between the estrogen and progesterone receptors on the gonads, as well as the androgen receptor on the ovary, have not been determined so there are connections of unknown polarity between these receptors and the gonads.

B.5: DETAILS ON GA OPTIMIZATION OF M-MODEL

The parameters of the M-model were optimized using the genetic algorithm (GA) as implemented in the MATLAB Global Optimization Toolbox. A robust optimization procedure such as the GA is appropriate because the M-model is both nonlinear (sigmoidal squashing function for unit activations) and discontinuous (hard limit of zero for monoaminergic transmitter levels). The 76 real-valued parameters were 23 receptor strengths (on monoaminergic units), 18 connection weights (onto and between non-monoaminergic units), 3 monoaminergic transporters, 29 drug effects (most of the drugs have multiple targets), and 6 biases (one for each monoaminergic and non-monoaminergic unit). The 76 parameters form a parameter set that was organized as a vector of 76 elements, where each element is a different parameter. Each run of the GA maintained a population of 100 parameter sets (parameter vectors) and was allowed to "evolve" through simulated mutation and recombination over many generations until the change in fitness between generations was less than a tolerance set to 10^{-12}.

We minimized an inverse fitness function (error function) that was based mainly on the difference between the behavior of the monoaminergic units in the M-model and that of real monoaminergic neurons in their responses to acute administration of various drugs targeting the monoaminergic neurotransmitter systems in rats (Dong and Blier 2001, Szabo and Blier 2001, Chernoloz, El Mansari et al. 2009, Katz, Guiard et al. 2010, Ghanbari, El Mansari et al. 2012, El Mansari, Manta et al. 2015, Oosterhof, El Mansari et al. 2015). The rats in these studies were normal, and were not subjected to stressors or other manipulations designed to evoke a depressive phenotype (ibid). The drugs and drug combinations included in the error function constitute the set of drugs that target the monoaminergic neurotransmitter systems studied by Pierre Blier and his lab, with the exceptions of GBR12909 (GBR) and Pramipexole (PPX).

GBR is a high-affinity DA reuptake inhibitor, with 500-fold higher affinity for the dopamine transporter (DAT) than for the other monoaminergic transporters (Andersen 1989). It does not have significant affinity for any other receptors (TOCRIS , Andersen 1989, Rothman, Mele et al. 1991). The Blier group found a 26% decrease in VTA DA neuron firing in response to acute GBR, with no change in the firing parameters of LC NE neurons or DR 5HT neurons (Katz, Guiard et al. 2010). This is inconsistent with the behavior of the other reuptake blockers, Escitalopram, Nomifensine, and Reboxetine, which all produce changes in neuronal firing rate in more than one monoaminergic region (Katz, Guiard et al. 2010, Chernoloz, El Mansari et al. 2012).

During GA searches, the strength of GBR was repeatedly pushed to zero by the algorithm. Due to inconsistency of GBR data with the behavior of the other reuptake inhibitors, as well as consistent GA assignment of zero strength for GBR in the M-model, data obtained from GBR experiments was removed from the error function and was not considered further in M-model analysis.

PPX primarily targets D3 receptors (D3R) (Mierau, Schneider et al. 1995). PPX has been found to be 8 times more potent as a D3 receptor agonist than as a D2 receptor agonist through functional measurements of receptor activation (Mierau, Schneider et al. 1995). The dissociation constant (Ki) of PPX is 0.5 nM at D3R and 3.9 nM at D2R, demonstrating that the binding affinity of PPX at D3R is almost 8 times higher than that of PPX at D2R (Newman-Tancredi, Cussac et al. 2002). D3Rs are mainly expressed in the nucleus accumbens, hypothalamus, and prefrontal cortex, but are not present in significant levels in the monoaminergic regions (Levesque, Diaz et al. 1992). In the M-model, receptors are represented explicitly only on monoaminergic units, so D3Rs are not represented. PPX data was not included in the error function nor was it considered in M-model analysis because its primary target, D3R, is not represented in the M-model.

Interpretations of data by different groups ascribe to Bupropion a mechanism of action that elevates NE and DA through either a releasing (Dong and Blier 2001) or reuptake blocking (NDRI) mechanism (Cooper, Wang et al. 1994). The Blier lab adheres to the releasing mechanism interpretation, which is the mechanism that is implemented in the M-model. To study the effects of Quetiapine, the Blier lab used a compound combination they called "human Quetiapine." Because humans metabolize Quetiapine to N-Desalkyl quetiapine (Nquet) but rodents do not, rodents were given a mixture of Nquet and Quetiapine in the ratio present in humans during the metabolism of quetiapine to produce human Quetiapine (Chernoloz, El Mansari et al. 2012). We simulated the effects of human Quetiapine in the M-model by giving Quetiapine all the targets of both Quetiapine and Nquet.

The error function that was minimized by the GA computed a modified root mean square (RMS) error. The heart of the error function is the differences between the observed percentage changes and the percentage changes in the average activation levels of the monoaminergic units in the M-model due to acute drug administration, as described above. Acute drug data were obtained from the experimental findings of the Blier group. Through reduction of error, the GA had to optimize several criteria in addition to the agreement in the percentage changes in monoaminergic activation levels due to acute drugs. The baseline (no-drug) activity levels of the

6 units were required to be near 0.50, which is the midpoint of the unit activity range as governed by the squashing function. This gave the units maximal freedom to increase or decrease their activations with drug administrations or TSC strength adjustments. Monoaminergic baseline (no-drug) neurotransmitter levels had to be 0.10 or greater. This ensured that pre-drug transmitter levels were high enough for all drugs to have a substantial effect. The rise in 5HT following acute Escitalopram had to be 0.20 or greater, and the rise in NE following acute Reboxetine had to be 0.20 or greater. This ensured that levels of 5HT and NE due to acute blockade of their respective transporters agreed with experimental findings (Kreiss and Lucki 1995, Malagie, Trillat et al. 1995, Bymaster, Zhang et al. 2002, Page, Brown et al. 2003, Romero, Celada et al. 2003).

In the error function, differences in the no-drug monoaminergic unit activations from 0.5, and differences between the observed and simulated monoaminergic activation percentage changes due to acute drug, were expressed as actual RMS differences (i.e., RMS errors). However, each no-drug monoaminergic transmitter level below 0.1, and each 5HT or NE level below 0.2 with acute Escitalopram or Reboxetine, respectively, conditionally contributed a value of 100 to the error term for the offending parameter set. Because discrepancies between desired and simulated transmitter levels were expressed as conditionals, our error function computed a modified RMS error measure.

For programming convenience, parameters whose values could be positive or negative (i.e., strengths of receptors, transporters, and drugs) were set as absolute values and their signs were fixed in program code. Other parameters (i.e., generic weights and unit biases) were signed by the optimization procedure. Lower and upper bounds for the parameter values in the GA were set by hand. Lower and upper bounds for the generic weights of the connections onto non-monoaminergic transmitter units, and for all unit biases, were set at −10 and +10. Lower and upper autoreceptor bounds were set at 3 and 10, respectively. The GA-determined levels for all autoreceptors (DR 5HT1A, LC AR2, and VTA D2R) were near 3 in almost all 200 parameterizations and in all of the “ten-best” parameterizations. All other receptor bounds were set at 1 and 10. Transporter bounds were set at 0.3 and 0.9. Bounds for the strengths of the drugs were set at 0 and 1. The bounds on the strengths of drugs provided consistency in effects for drugs of different classes in the M-model.

All receptors contributed a component to net input equal to the product of their strength and the level of their cognate transmitter, regardless of whether or not a drug that affects them was

present. Agonist drugs add a contribution from a receptor equal to the product of the receptor strength and the drug strength. Antagonist drugs subtract a component equal to the product of the receptor strength, the drug strength, and the level of the cognate transmitter. Because transmitters and drugs are bounded between 0 and 1, this scheme ensures that an agonist drug can increase the receptor contribution at most by one full receptor strength, while an antagonist can decrease the receptor contribution at most to zero. Transporter blocking drugs worked similarly, reducing the level of a transporter by an amount equal to the product of the transporter strength and the drug strength. Therefore, a blocker could reduce the strength of a transporter at most to zero. Transmitter releasing drugs add a contribution of neurotransmitter to the unit activation level equal to the product of the amount of released transmitter (which is equal to the unit activation) and the drug strength. Because the releasing drug strengths (like all drug strengths) are bounded between 0 and 1, this ensures that a releasing drug can at most double the amount of released transmitter.

The 10 lowest-error parameter sets of the 200 GA searches were separated out for further consideration. For all of these "ten best" parameterizations, the transmitter levels achieved their required levels. Therefore, the conditional contributions to the error functions were zero, leaving only the actual RMS differences in desired and actual monoaminergic unit activities. Note that the purpose of the GA optimization was to set baseline parameter values according to the data on the acute effects of drugs. Data on chronic drug effects, which involve adjustments in baseline receptor values, were therefore not represented in the fitness function.

B.6: SUMMARY OF DRUGS AND DRUG COMBINATIONS CONSIDERED IN THE M-MODEL

Each row contains the name of a drug, its class, current uses, its effects as represented in the M-model, and supporting references. These drugs and drug combinations were used in the experiments by the Blier lab that determined the percent changes from baseline in the firing rates of neurons in the monoaminergic nuclei after acute (2-day) and chronic (14-day) drug administration. The drug types include transporter blockers, receptor agonists, receptor antagonists, and neurotransmitter releasers. The strengths of each of these drugs at their targets were determined using the GA implemented in MATLAB.

Drug name	Drug class	Drug uses	Drug effects at targets	References
Escitalopram	2nd generation antidepressant	Depression	5HT transporter blocker	(Sanchez, Bergqvist et al. 2003, Chen, Larsen et al. 2005)
Nomifensine	2nd generation antidepressant	Depression	DA, NE and 5HT transporter blocker	(Brogden, Heel et al. 1979, Tatsumi, Groshan et al. 1997)
Reboxetine	2nd generation antidepressant	Depression, panic disorder, attention deficit hyperactivity disorder (ADHD)	NE transporter blocker	(Page, Brown et al. 2003, Hajos, Fleishaker et al. 2004)
Trazodone	Tetracyclic antidepressant	Depression, post-traumatic stress disorder (PTSD), insomnia	5HT transporter blocker, agonist at 5HT1AR, antagonist at 5HT2AR, 5HT2CR, AR1, AR2, and D2R	(Cusack, Nelson et al. 1994, Nierenberg, Adler et al. 1994, Krege, Goepel et al. 2000, Balsara, Jadhav et al. 2005, Odagaki, Toyoshima et al. 2005, Stahl 2009, Stahl 2009)
Asenapine	Atypical antipsychotic	Bipolar disorder, schizophrenia	Agonist at 5HT1AR, antagonist at 5HT2AR, AR2, and D2R	(Ghanbari, El Mansari et al. 2009, Bjorkholm, Franberg et al. 2015)
Aripiprazole	Atypical antipsychotic	Bipolar disorder, schizophrenia	Agonist at 5HT1AR and D2R, antagonist at 5HT2AR and 5HT2CR	(Shapiro, Renock et al. 2003, Li, Ichikawa et al. 2004, Han, Wang et al. 2013)

Bupropion	Atypical antidepressant	Depression, seasonal affective disorder	Releaser of NE and DA	(Cooper, Wang et al. 1994, Cusack, Nelson et al. 1994, Dong and Blier 2001, El Mansari, Ghanbari et al. 2008)
Quetiapine	Atypical antipsychotic	Bipolar disorder, schizophrenia, depression	NE transporter blocker, agonist at 5HT1AR, antagonist at 5HT2AR, AR1, AR2, D1R, and D2R	(DeVane and Nemeroff 2001, Jensen, Rodriguiz et al. 2008, Han, Wang et al. 2013)

B.7: MS-MODEL TRUTH-TABLE JUSTIFICATION

The MS-model was trained on baseline values and to reproduce data on the effects of neuron activations, transmitter, enzyme, and hormone levels of acute receptor blockade, lesions, and other experimental manipulations. All of the manipulations (drug or hormone administration, chemical lesioning, etc.) will be referred to as "inputs." For the purposes of training the model the training data were assembled into an input-output table or "truth table" in which the inputs are acute drug administrations, and the outputs are changes from baseline firing-rate of the monoaminergic neurons expressed as a percentage. Data on the effects of inputs on model unit activations were obtained through an extensive literature search that compiled findings from multiple groups using a broad range of experimental methods. Training data were for 40 single inputs and 25 combination inputs. Each row of the truth table represents the results of one or more actual experiments where output levels were measured in response to one or more inputs. Inputs are either present or absent (0 or 1) and outputs are assigned integer values between 0.30 (lowest) to 0.70 (highest). Output findings from the literature and their corresponding integer values are shown in the table below. All outputs bound between 0 and 1 by the sigmoidal squashing function.

0.30	0.40	0.50	0.60	0.70
Decrease maximally	Decrease moderately	No change	Increase moderately	Increase maximally

Determinations of "moderate" versus "maximal" changes were made based on both the qualitative and quantitative data that was available. When more than one finding was available on a particular input-output relationship, a consensus was reached using the available data. If neurotransmitter level changes differed in different brain regions, the change in the level of the neurotransmitter in the prefrontal cortex (PFC) was used in the truth table. If whole brain neurotransmitter level change was available, then the effect of the input on whole brain neurotransmitter level was used in the truth table. If neurotransmitter level change data for the whole brain or PFC was not available, then the change in the neurotransmitter level of the brain regions that were available was used to determine the truth-table value with that input. This subjective approach was necessary to account for differences between research labs in experimental methods, drug dosages and routes of administration, and levels of quantification. The majority of the findings were derived from rodent studies but some were obtained from horse, monkey, cat, cow, fish, squirrel and human studies.

The first single-input is an SSRI, which consolidates the findings associated with acute administration of several different SSRIs. Although different SSRIs have different low-affinity off-target effects, all of them have strong affinity for the 5HT transporter, which is the only structure connection from the SSRI input included in the model (Tatsumi, Groshan et al. 1997, Sanchez, Bergqvist et al. 2003). Binding of the SSRI to the 5HT transporter leads to a doubling of extracellular 5HT, so the output for 5HT with acute SSRI was set to 0.60 (Invernizzi, Belli et al. 1992, Koch, Perry et al. 2002, Calcagno, Guzzetti et al. 2009). Because acute administration of SSRIs other than fluoxetine does not significantly change NE and DA levels, the truth table values for these neurotransmitters were set to 0.50 (Bymaster, Zhang et al. 2002, Koch, Perry et al. 2002).

The increase in extracellular 5HT associated with acute SSRI administration has been associated with increased binding to the 5HT1A autoreceptor on DR neurons, decreasing the firing activity of these neurons (Calcagno, Guzzetti et al. 2009). The Blier group and others have found that the DR neuron firing rate decreases by about 65% with acute SSRI, so the truth table value for this output was set to 0.40 (de Montigny, Chaput et al. 1990, Czachura and Rasmussen 2000, Chernoloz, El Mansari et al. 2012). The Blier group found that acute SSRI administration decreases the firing rate of LC neurons by 45% and decreases the firing rate of VTA neurons by

41%, so the truth table values for the LC and VTA firing rates with acute SSRI were also set to 0.40 (Chernoloz, El Mansari et al. 2009, Dremencov, El Mansari et al. 2009, Chernoloz, El Mansari et al. 2012). fMRI studies indicate that amygdala activity decreases moderately, while cortical activity does not change with acute SSRI administration (Mayberg, Brannan et al. 2000, Kennedy, Evans et al. 2001, Takahashi, Yahata et al. 2005, Murphy, Norbury et al. 2009). The Murphy lab found that amygdala activity decreases moderately in response to neutral faces with acute SSRI, and the Mayberg lab found that PFC activity increases after 6-weeks of SSRI treatment but not after acute (1-week) SSRI treatment. The truth table values for the amygdala and PFC with acute SSRI are set to 0.40 and 0.50, respectively.

Acute SSRI administration has been found to stimulate the rodent HPA axis by increasing CRF, ACTH, and cortisol levels while also increasing PVN activity (Jensen, Jessop et al. 1999, Wieczorek, Schulz et al. 2001, Hesketh, Jessop et al. 2005). Specifically, 30 minutes of subcutaneous cannula citalopram administration maximally increases cortisol and ACTH levels (Jensen, Jessop et al. 1999). This lab also found that PVN activity increases moderately as measured by the percentage of c-Fos immunoreactive cells in the PVN. The same lab did not find a significant difference in CRF mRNA with acute citalopram treatment; however, another lab found that acute citalopram moderately increases CRF levels (Moncek, Duncko et al. 2003). The Moncek lab also found that acute citalopram produces very large increases in cortisol and ACTH levels. The truth table values for ACTH and cortisol with acute SSRI was both set to 0.70. The truth table value for CRF with acute SSRI was set to 0.60 to reflect the moderate increase in CRF found by the Moncek lab and the finding that cortisol and ACTH levels increase maximally. Oxytocin levels have been found to moderately increase with acute SSRI, while arginine-vasopressin (AVP) levels have been found to stay the same (Hesketh, Jessop et al. 2005). We set the oxytocin target to 0.60 and the AVP target to 0.50 with acute SSRI. Acute fluoxetine injection moderately increases galanin mRNA levels, so the truth-table value for galanin with acute SSRI was set to 0.60 (Kuteeva, Wardi et al. 2008).

The second single-input is Nomifensine, a reuptake blocker of the NE and DA transporter proteins, with slight affinity for the 5HT transporter (Samanin, Bernasconi et al. 1975, Brogden, Heel et al. 1979, Tatsumi, Groshan et al. 1997). The Blier group found that acute administration of Nomifensine increases DR neuron activity by 50%, decreases VTA neuron activity by 39%, and decreases LC neuron activity by 71% (Katz, Guiard et al. 2010). The truth-table values for the

acute effect of Nomifensine on DR, LC and VTA neurons were therefore set to 0.60, 0.40, and 0.40, respectively. The Masana lab found that acute Nomifensine maximally increases DA levels, but the Samanin lab found that acute Nomifensine did not significantly change DA levels (Samanin, Bernasconi et al. 1975). The Carboni lab found that acute Nomifensine increases DA levels by a very large amount (Carboni, Imperato et al. 1989). The Butcher lab found a moderate increase in DA levels with acute Nomifensine (Butcher, Fairbrother et al. 1988). Because some labs report a maximal increase in DA with acute Nomifensine while others do not detect any change in DA levels, the truth-table value for DA with acute Nomifensine was set to 0.60 to reflect a moderate increase in DA.

Reboxetine is a selective NE transporter blocker (Hajos, Fleishaker et al. 2004). The Blier group found that acute Reboxetine administration decreases LC firing rate by 68% without affecting DR firing rate (Szabo and Blier 2001). They also found that acute Reboxetine administration decreases VTA neuron firing rate by 31% (Katz, Guiard et al. 2010). The truth-table values for acute Reboxetine for DR, LC, and VTA were therefore set to 0.50, 0.40, and 0.40, respectively. Acute Reboxetine administration doubles NE levels and produces a moderate increase in DA levels while producing no change in 5HT levels, corresponding to values of 0.60, 0.60, and 0.50 in the truth table for these neurotransmitters, respectively (Page and Lucki 2002). One fMRI study in humans shows that acute Reboxetine administration moderately decreases amygdala response to neutral stimuli, so the truth-table value for the amygdala with acute Reboxetine was set to 0.40 (Onur, Walter et al. 2009). Acute Reboxetine administration in humans has been found to moderately increase ACTH levels in two studies using male volunteers, so the truth-table value for ACTH with acute Reboxetine was set to 0.60. Acute Reboxetine administration has also been shown to moderately increase cortisol levels in two different studies using male human volunteers, so the truth-table value for cortisol with acute Reboxetine was set to 0.60 (Hennig, Lange et al. 2000, Schule, Baghai et al. 2004).

Trazodone is a multifunctional drug that blocks the 5HT transporter and interacts with multiple monoaminergic receptors (Stahl 2009, Stahl 2009). The Blier lab found that acute Trazodone administration decreases DR neuron firing by 65%, increases LC neuron firing by 25%, and does not alter VTA neuron firing (Ghanbari, El Mansari et al. 2010, Ghanbari, El Mansari et al. 2012). We set the target output values for DR, LC, and VTA with acute Trazodone to 0.40, 0.60, and 0.50, respectively. Acute Trazodone administration has been found to double 5HT levels

without changing NE levels, so the truth-table values for these were set to 0.60 and 0.50, respectively (Rowbotham, Jones et al. 1984, Pazzagli, Giovannini et al. 1999).

Asenapine is an antipsychotic drug that interacts with multiple monoaminergic receptors (Franberg, Wiker et al. 2008, Ghanbari, El Mansari et al. 2009). The Blier group found that acute Asenapine administration decreases DR neuron firing by about 30% without affecting the firing rates of the LC or VTA (Oosterhof, El Mansari et al. 2015). We set the truth table values for DR, LC, and VTA to 0.40, 0.50, and 0.50. Acute Asenapine administration in rats has been found to moderately increase 5HT, NE, and DA levels (Franberg, Marcus et al. 2009). The truth table outputs for 5HT, NE, and DA with acute Asenapine were all set to 0.60.

Aripiprazole is an antipsychotic drug with strong affinity for DA and 5HT receptors (Shapiro, Renock et al. 2003). The Blier group found that acute Aripiprazole administration increases DR neuron firing rate by 48%, without affecting the firing rates of LC or VTA neurons (Chernoloz, El Mansari et al. 2009). The truth-table values for the DR, LC and VTA were set to 0.60, 0.50 and 0.50, respectively. Acute Aripiprazole administration has been found to moderately increase DA levels in experiments done by Zocchi et al and Li et al without affecting 5HT, NE, or cortisol levels (Li, Ichikawa et al. 2004, Zocchi, Fabbri et al. 2005, Assie, Carilla-Durand et al. 2008). The truth-table values for 5HT, NE, DA, and cortisol were set to 0.50, 0.50, 0.60, and 0.50 with acute Aripiprazole, respectively.

Bupropion is an antidepressant drug that blocks the NE and DA transporter proteins (Cooper, Wang et al. 1994, Stahl, Pradko et al. 2004). The Blier group found that acute Bupropion administration doubles DR neuron firing rate, decreases LC neuron firing rate by half, and does not change VTA neuron firing rate (El Mansari, Ghanbari et al. 2008). Another group found that acute Bupropion moderately decreases LC and VTA neuron firing rate (Cooper, Wang et al. 1994). The truth-table values for the DR, LC and VTA were set to 0.60, 0.40 and 0.40, respectively, with acute Bupropion administration. Acute Bupropion administration has been found to moderately increase DA and NE levels without affecting 5HT levels (Piacentini, Clinckers et al. 2003). The truth-table values for 5HT, NE, DA were set to 0.50, 0.60, and 0.60 with acute Bupropion.

Quetiapine is an antipsychotic drug with multiple receptor and transporter targets, including the dopamine D2 receptor, the 5HT2A receptor, and the alpha-1 adrenergic receptor (AR1) (DeVane and Nemeroff 2001, Jensen, Rodriguiz et al. 2008). The Blier group found that acute Quetiapine administration decreases the DR neuron firing rate by 43% and increases the LC

neuron firing rate by 40% (Chernoloz, El Mansari et al. 2012). The truth-table values for the DR and LC with acute Quetiapine were set to 0.40 and 0.60, respectively. Another group found that acute Quetiapine moderately increases VTA firing rate, so the truth-table value for the VTA with acute Quetiapine was set to 0.60 (Werkman, Olijslagers et al. 2004). Denys et al found that acute Quetiapine moderately increases 5HT and DA levels in the PFC, while Silverstone et al found that acute Quetiapine has no effect on 5HT levels, but moderately increases NE and DA levels (Denys, Klompmakers et al. 2004, Silverstone, Lalies et al. 2012). The truth table values for 5HT, NE, and DA with acute Quetiapine were all set to 0.60.

Pramipexole (PPX) is a D2, D3, and D4 receptor agonist (Mierau, Schneider et al. 1995). The Blier group found that acute PPX administration does not change DR neuron firing rate, decreases LC neuron firing rate by 33%, and decreases VTA neuron firing rate by 40% (Chernoloz, El Mansari et al. 2009). The truth-table values for the DR, LC and VTA were therefore 0.50, 0.40 and 0.40 with acute PPX administration.

GBR12909 (GBR) is a DA transporter blocker (TOCRIS , Andersen 1989, Singh 2000). The Blier group found that acute GBR administration does not change DR or LC neuron firing rate but decreases VTA neuron firing rate by 26% (Katz, Guiard et al. 2010). Another group found a similar decrease of about 25% in VTA neuron firing rate with acute GBR (Choong and Shen 2004). The truth-table values for the DR, LC and VTA were set to 0.50, 0.50 and 0.40, respectively, with acute GBR administration. Three groups have found moderate increases in DA levels with acute GBR, so the truth-table value of DA with acute GBR was set to 0.60 (Rothman, Mele et al. 1991, Choong and Shen 2004, Masana, Bortolozzi et al. 2011).

Clozapine is an antipsychotic drug that targets many serotonergic, noradrenergic, and dopaminergic receptors (Meltzer 1994). Acute administration of Clozapine has been found to moderately decrease the firing activity of DR neurons, moderately increase the firing rate of LC neurons, moderately increase the firing rate of VTA neurons, and moderately increase the firing activity of PFC neurons (Souto, Monti et al. 1979, Sprouse, Reynolds et al. 1999, Chen and Yang 2002, Gao 2007). Another group found that acute Clozapine completely inhibits DR firing activity, however, the dose that was used was much higher than the standard rodent dose (Gallager and Aghajanian 1976). The truth-table values for DR, LC, VTA, and PFC were set to 0.40, 0.60, 0.60, and 0.60, respectively. Acute Clozapine administration has been found by Zocche et al to maximally increase NE levels and moderately increase DA levels. Masana et al also found that

Clozapine moderately increases DA levels. Lee et al 2001 found that Clozapine moderately increases cortisol levels in awake humans, so the truth table value for NE was set to 0.70 and the truth table values for DA and cortisol were set to 0.60 (Zocchi, Fabbri et al. 2005, Masana, Bortolozzi et al. 2011). One group has found that Clozapine decreases 5HT release in the nucleus accumbens, while another found that Clozapine increases 5HT in the nucleus accumbens and the PFC (Ferre and Artigas 1995, Ichikawa, Kuroki et al. 1998). Because these two groups found opposing effects of Clozapine on 5HT, and a third group found that 5HT does not change in the PFC with acute Clozapine, we used a truth-table value of 0.50 for 5HT with acute Clozapine (Zocchi, Fabbri et al. 2005).

Ketamine is an antagonist at N-methyl-D-asparatate (NMDA) receptors (Hall and Murdoch 1990). The Blier group found that acute Ketamine administration does not change DR or VTA neuron firing rate but increases LC neuron firing rate by 23% (El Iskandrani, Oosterhof et al. 2015). The truth-table values for the DR, LC and VTA were set to 0.50, 0.60, and 0.50, respectively, with acute Ketamine administration. Razoux et al found that Ketamine moderately increases PFC neuron activity and moderately increases extracellular glutamate. Stone et al also found that Ketamine moderately increases anterior cingulate glutamate, so the truth-table value for the PFC and glutamate were set to 0.60 (Razoux, Garcia et al. 2007, Stone, Dietrich et al. 2012, Pehrson and Sanchez 2014, Bjorkholm, Franberg et al. 2015). Nishitani et al found that Ketamine moderately increases PFC 5HT levels, so the truth table value for 5HT was set to 0.60 with acute Ketamine. Stone et al and Lindeforsa et al both found that Ketamine has no effect on GABA levels, so the truth table value for GABA was set to 0.50 with acute Ketamine. Glisson et al found that acute Ketamine had no effect on rabbit whole brain NE or NE levels in any of the brain areas examined, so the truth table value for NE with acute Ketamine was set to 0.50. Glisson et al also found that DA levels did not change in rabbit whole brain with Ketamine, but did find a moderate increase in thalamus and hypothalamus DA. Lindeforsa et al found that acute Ketamine moderately increases DA levels in rat PFC. Because whole brain neurotransmitter level change is the standard criterion for the truth table, the truth-table value for DA with Ketamine was set to 0.50.

Reserpine depletes monoamines by inhibiting the activity of the vesicular monoamine transporter 2 (VMAT2), which transports monoamines to the cell membrane for release into the extracellular space (Scherman and Henry 1984, Rudnick, Steiner-Mordoch et al. 1990). Because VMAT2 is not an element in our model, Reserpine sends inhibitory projections directly to 5HT,

NE and DA. Reserpine maximally decreases 5HT, NE, and DA levels, so the truth-table values for 5HT, NE, and DA were all set to 3 (Cooper, Wang et al. 1994). Cooper et al found that Reserpine did not affect LC neuron firing rate, so the truth table value for LC with acute Reserpine was set to 0.50. Baraban et al found that Reserpine moderately increases DR activity, then suppresses DR activity after about 30 minutes (Baraban, Wang et al. 1978, Baraban and Aghajanian 1980). Because we are interested in the immediate, acute effect of Reserpine, we set the truth-table value for DR with acute Reserpine to 0.60. An injection of Reserpine in cows produces no change in cortisol levels, so the truth-table value for cortisol was set to 0.50 for Reserpine (Bauman, Collier et al. 1977). The combination of Reserpine and Buproprion produces no change in the firing rate of LC neurons, so the truth-table value for LC with Reserpine/Bupropion was set to 0.50 (Cooper, Wang et al. 1994).

Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) (Roseboom and Kalin 2000). The Blier group found that Venlafaxine decreases DR firing rate by 47% and decreases LC firing rate by 21%, so the truth-table values for DR and LC were both set to 0.40 (Gartside, Umbers et al. 1997). Because acute Venlafaxine administration moderately increases the firing activity of the PFC in a c-fos study, we set the truth-table value for PFC with Venlafaxine to 0.60 (Higashino, Ago et al. 2014). Higashino et al found that acute Venlafaxine administration moderately increases 5HT in the PFC, moderately increases NE in the PFC, and maximally increases DA in the PFC and Beyer et al found that acute Venlafaxine has no effect on 5HT levels but maximally increases NE levels in the PFC (Beyer, Boikess et al. 2002, Higashino, Ago et al. 2014). The truth-table value for 5HT was set to 0.60 to reflect a moderate increase due to Venlafaxine's 5HT transporter inhibition. The truth-table values for NE and DA were both set to 0.70 to reflect the large increases in the levels of these neurotransmitters with acute Venlafaxine observed by the Higashino and Beyer groups.

Desipramine is a tricyclic antidepressant with strong affinity for the NE transporter and weaker affinity for the 5HT and DA transporters as well as affinity for various monoaminergic receptors (Berti and Shore 1967). DR firing was found to moderately decrease with acute Desipramine, so the truth-table value for DR was set to 0.40 with acute Desipramine (Gartside, Umbers et al. 1997). Acute Desipramine also moderately decreases LC neuron activity, so the truth-table value for LC was set to 0.40 (Scuvee-Moreau and Dresse 1979). Acute administration of Desipramine was found by Beyer et al to maximally increase NE levels without changing 5HT

levels, and Kreiss et al also found that Desipramine has no effect on 5HT levels (Kreiss and Lucki 1995, Beyer, Boikess et al. 2002). Higashino et al found no change in 5HT levels with acute Desipramine, but found a maximal increase in NE levels and a moderate increase in DA levels (Kreiss and Lucki 1995, Higashino, Ago et al. 2014). The truth-table value for 5HT was set to 0.50, for NE was set to 0.70, and for DA was set to 0.60. Acute Desipramine was found to have no effect on PFC activity, so this truth-table value was set to 0.50 (Higashino, Ago et al. 2014). Desipramine injection in humans moderately increases blood cortisol levels after 30 minutes, so the truth-table value for cortisol with Desipramine was set to 0.60 (Asnis, Halbreich et al. 1985).

CP-96345 (CP) is a neurokinin-1 receptor antagonist (Fong, Yu et al. 1992). The Blier group found that acute administration of CP increases the firing rate of DR neurons by 46% but does not affect the firing rate of LC neurons, so the truth-table values for DR and LC were set to 0.60 and 0.50 for the DR and LC with acute CP, respectively (Conley, Cumberbatch et al. 2002, Haddjeri and Blier 2008). Lejeune et al found that NK1 receptor antagonists moderately enhance VTA firing rate, so the truth-table value for VTA with acute CP was set to 0.60. Lejeune et al also found that NK1 receptor antagonists have no effect on 5HT levels, so the 5HT value with acute CP was set to 0.50. Renoldi et al found that acute CP has no effect on NE levels, but moderately increases DA levels in the PFC of gerbils. Lejeune et al also found a moderate increase in DA levels with acute NK1 receptor antagonists. The truth table value for NE was set to 0.50 and for DA was set to 0.60 with acute CP (Lejeune, Gobert et al. 2002, Renoldi and Invernizzi 2006, Guiard, Guilloux et al. 2007). Renoldi et al also found that the combination of NK1 antagonists and stress leads to no change in NE or DA levels (Renoldi and Invernizzi 2006). The truth-table values for NE and DA with CP/Stress were set to 0.50.

Gepirone is an agonist of 5HT1A receptors (Blier and Ward 2003). The Blier group and others have found that acute administration of 5HT1A agonists maximally decrease DR neuron firing rate, so the truth-table value of DR with Gepirone was set to 0.30 (VanderMaelen, Matheson et al. 1986, Blier and de Montigny 1987, Blier and de Montigny 1990). 5HT1A receptor agonists have been found to maximally decrease 5HT levels by multiple groups, so the truth table value for 5HT with acute Gepirone was set to 0.30 (Rutter, Gundlah et al. 1994, Dawson, Nguyen et al. 2002). 5HT1A receptor agonists have also been found to moderately increase CRF, ACTH, and cortisol release in rodents, so the truth-table values for CRF, ACTH, and cortisol with acute Gepirone were set to 0.60 (Pan and Gilbert 1992, Matheson, Knowles et al. 1997). The

combination of Gepirone and stress also moderately increases cortisol levels, so the cortisol level in the truth-table with acute Gepirone/stress was set to 0.60 (Matheson, Knowles et al. 1997). The combination of Gepirone/Dexamethasone moderately decreases cortisol levels, so the cortisol level in the truth-table with acute Gepirone/Dexamethasone was set to 0.40 (Matheson, Knowles et al. 1997).

RU-28362 (RU) is a glucocorticoid receptor agonist (Sernia and Thomas 1994). Administration of RU alone does not change ACTH levels, so the truth-table value for ACTH with acute RU was set to 0.50 (Hinz and Hirschelmann 2000).

Org-34850 (Org) is a glucocorticoid receptor antagonist (Reynolds, Saunders et al. 2015). Glucocorticoid receptors mediating negative feedback on the HPA axis are present in the hypothalamus, pituitary gland, and adrenal gland (among others) (Loose, Do et al. 1980, Morimoto, Morita et al. 1996, Ozawa, Ito et al. 1999). Acute Org administration by itself has been found by Spiga et al 2007 and Spiga et al 2008 to have no effect on cortisol levels, so the truth-table value for cortisol with acute Org was set to 0.50. Acute Org/Stress was also found by this group to have no effect on cortisol levels, so the truth-table value for cortisol with acute Org/Stress was set to 0.50.

Oxytocin is an input that projects to oxytocin receptors in the model (Gimpl and Fahrenholz 2001). Oxytocin administration to rats has been shown to double DA levels, so the truth-table value for DA was set to 0.60 (Melis, Melis et al. 2007). Oxytocin by itself as well as Oxytocin/Stress had no effect on PVN CRF mRNA, so the CRF value with Oxytocin and with Oxytocin/Stress was set to 0.50 (Bulbul, Babygirija et al. 2011). Oxytocin has been found to moderately decrease amygdala response to fearful stimuli (faces and scenery), so the truth-table value for amygdala with Oxytocin/Stress was set to 0.40 (Kirsch, Esslinger et al. 2005). One study in rats from 1984 found that Oxytocin does not have a significant effect on ACTH levels, however, because several other groups since 1984 have found that Oxytocin moderately decreases ACTH in both humans and monkeys, the truth-table value for ACTH with Oxytocin was set to 0.40 (Gibbs, Vale et al. 1984, Chiodera and Coiro 1987, Parker, Buckmaster et al. 2005). It has also been found that Oxytocin moderately decreases cortisol levels, so the truth-table value for cortisol with Oxytocin was set to 0.40 (Legros, Chiodera et al. 1984).

Dexamethasone is a corticosteroid with significant affinity for glucocorticoid receptors but not mineralocorticoid receptors in vivo (Bamberger, Bamberger et al. 1995, Reul, Gesing et al.

2000, Pariante and Miller 2001). Rush et al found that Dexamethasone maximally suppresses cortisol levels, so the truth-table value for cortisol with Dexamethasone was set to 0.30 (Rush, Giles et al. 1996). Kovacs et al found that Dexamethasone maximally suppresses PVN CRF mRNA, so the truth-table value for CRF with Dexamethasone was set to 0.30 (Kovacs and Mezey 1987). Hohnloser et al found that acute Dexamethasone administration moderately decreases ACTH levels, so the truth-table value for ACTH with Dexamethasone was set to 0.40 (Hohnloser, Von Werder et al. 1989). Kovacs et al found that acute Dexamethasone moderately decreases AVP mRNA in the PVN, so the truth-table value for AVP with Dexamethasone was set to 0.40 (Kovacs and Makara 1988). C-Fos mRNA responses in the PVN and pituitary gland were found to be moderately decreased with acute Dexamethasone, so the truth-table values for the PVN and pituitary gland were set to 0.40 (Karssen, Meijer et al. 2005). Dexamethasone has been shown to interact with the monoamines. Specifically, Dexamethasone administration has been shown to moderately increase the levels of 5HT precursors and 5HT, so the truth-table values for Trp, 5HTP, and 5HT were set to 0.60 with Dexamethasone (Maes, Meltzer et al. 1995, Tsubota, Adachi et al. 1999, Clark, Flick et al. 2008). Dexamethasone has also been found to moderately increase the levels of extracellular DA but moderately decrease extracellular NE, so the truth-table values for DA and NE were set to 0.60 and 0.40, respectively (Stene, Panagiotis et al. 1980, Tsubota, Adachi et al. 1999). Oxytocin levels were unaffected by Dexamethasone, so the truth table value for oxytocin with Dexamethasone was set to 0.50 (Fink, Robinson et al. 1988).

WAY-100635 (WAY) is a selective 5HT1A receptor antagonist (Fletcher, Forster et al. 1996). Administration of WAY has been shown to reverse the inhibitory effects of 5HT1A receptor agonists on DR firing rate, so the truth-table value for DR with WAY/Gepirone was set to 0.50 (Fletcher, Forster et al. 1996). WAY/Gepirone together has also been shown to prevent the rise in ACTH observed with Gepirone, so the truth-table value for ACTH with WAY/Gepirone was set to 0.50 (Fletcher, Forster et al. 1996). 5HT1AR antagonists by themselves moderately increase extracellular 5HT, so the truth-table value for 5HT with WAY was set to 0.60 (Arborelius, Nomikos et al. 1996).

Monoamine Oxidase Inhibitors (MAOI) block the activity of monoamine oxidase, which is an enzyme that mediates the breakdown of the monoamines (Stein 1960, Remick and Froese 1990). The Blier group found that acute MAOI administration moderately decreases DR and LC neuron firing without affecting VTA neuron firing, so the truth-table values for DR and LC were

set to 0.40 and the truth table value for VTA was set to 0.50 with MAOI (Blier and de Montigny 1985, Chenu, El Mansari et al. 2009). Acute MAOI administration has been shown to produce maximal increases in all 3 of the monoamines, so the truth-table values for 5HT, NE and DA were set to 0.70 (Butcher, Fairbrother et al. 1990, Celada and Artigas 1993, Kitaichi, Inoue et al. 2006).

Galanin is a 29 amino acid neuropeptide that is widely distributed in the central nervous system and co-secreted by DR and LC neurons (Tatemoto, Rokaeus et al. 1983). Agonists to the galR1 receptor (M-617) have been shown to have a pro-depressive effect, which is believed to be related to the inhibitory effect of galR1 receptors on DR and LC neurons (Sevcik, Finta et al. 1993, Larm, Shen et al. 2003, Wang, Li et al. 2016). Acute M-617 administration has been found to moderately decrease DR and LC firing rate and moderately decrease 5HT and NE levels (Jacobs, Wise et al. 1974, Azmitia and Segal 1978, Seutin, Verbanck et al. 1989, Sevcik, Finta et al. 1993, Yoshitake, Reenila et al. 2003, Hawes, Brunzell et al. 2005, Mazarati, Baldwin et al. 2005). We therefore set the truth-table values for DR, LC, 5HT, and NE to 0.40. It has also been found that M-617 administration produces moderate increases in the activities of the amygdala and PVN as measured by increases in c-fos expression in these regions, so the truth-table values for these regions were set to 0.60 (Blackshear, Yamamoto et al. 2007).

CRF1 receptor antagonists (CRF1R antagonist) block the CRF1 receptor to decrease HPA axis activity (Holsboer and Ising 2008). Specifically, it has been found by multiple labs that CRF1R antagonists moderately decrease ACTH and cortisol release, so the truth-table values for ACTH and cortisol with Antalarmin were set to 0.40 (Broadbear, Winger et al. 2004, Jutkiewicz, Wood et al. 2005, Ising and Holsboer 2007). It has also been found that acute administration of CRF1R antagonist/Stress moderately increases ACTH and cortisol, so the truth-table values for ACTH and cortisol for Antalarmin/stress was set to 0.60 (compared to +100% with stress alone) (Deak, Nguyen et al. 1999, Jutkiewicz, Wood et al. 2005).

Haloperidol is a dopamine D2 receptor antagonist (Schotte, Janssen et al. 1993). Subcutaneous haloperidol administration in rats produced no change in PFC NE or DA levels, so the truth table values for NE and DA with acute Haloperidol were set to 0.50 (Li, Perry et al. 1998). The combination of Haloperidol and Bupropion produced no change in the firing rate of VTA neurons, so the truth-table value for VTA with Haloperidol/Bupropion was set to 0.50 (Cooper, Wang et al. 1994).

Olanzapine is dopamine D2 receptor antagonist and 5HT2A receptor antagonist (Pilowsky,

Busatto et al. 1996). Subcutaneous Olanzapine administration in rats moderately increases PFC NE and DA levels, so the truth table values for NE and DA with acute Olanzapine were set to 0.60 (Li, Perry et al. 1998).

Clonidine is an α-2 receptor agonist (Unnerstall, Kopajtic et al. 1984). Administration of Clonidine has been found to moderately decrease LC neuron firing in rodents, and moderately decrease NE levels in humans (Veith, Best et al. 1984, Jacobs 1986). The truth-table values for LC and NE with acute Clonidine were set to 0.40.

Yohimbine is an alpha-2 receptor antagonist (Perry and U'Prichard 1981). Yohimbine administration in rats moderately elevates NE levels in the amygdala, so the truth-table value for NE with acute Yohimbine was set to 0.60 (Khoshbouei, Cecchi et al. 2002). The combination of Yohimbine and Stress maximally increase NE levels in the amygdala, so the truth-table value for NE with acute Yohimbine/Stress was set to 0.70 (Khoshbouei, Cecchi et al. 2002). The combination of Yohimbine/Stress was also found to moderately elevate galanin levels, so the truth-table value for galanin with Yohimbine/Stress was set to 0.60 (Khoshbouei, Cecchi et al. 2002).

The Blier group did a series of experiments where they lesioned one of the monoaminergic nuclei, then observed the change in the firing activity of the other two monoaminergic regions in order to determine how they influence one another. The results of these experiments are included in the truth table. Lesioning DR neurons maximally decreases 5HT levels, lesioning LC neurons maximally decreases NE levels, and lesioning VTA neurons maximally decreases DA levels (Guiard, El Mansari et al. 2008). The truth-table values of each were set to 0.30, respective to each lesion and neurotransmitter. DR lesion moderately increases LC and VTA firing rates (Haddjeri, de Montigny et al. 1997, Guiard, El Mansari et al. 2008, Ito, Shimogawa et al. 2014). The truth-table values for both LC and VTA with DR lesion were set to 0.60. LC lesion moderately increases VTA firing without changing DR firing rate (Gobbi, Cassano et al. 2007, Guiard, El Mansari et al. 2008). The truth-table values for VTA and DR with LC lesion were set to 0.60 and 0.50, respectively. VTA lesion moderately decreases DR firing rate and moderately increases LC firing rate (Guiard, El Mansari et al. 2008, Guiard, El Mansari et al. 2008). The truth table values for DR and LC with VTA lesion were set to 0.40 and 0.60, respectively.

The stress response begins with activation of the HPA axis, so the stress input sends an excitatory projection to the PVN (Sapolsky 2000, Gold and Chrousos 2002, de Kloet, Joels et al. 2005). Stress leads to maximal elevation of PVN activity as measured by induction of c-fos mRNA

expression (Cullinan, Herman et al. 1995). Stress also leads to maximal increases in the activity of the anterior pituitary gland and adrenal gland as measured by maximal blood flow increases after acute stress and c-fos induction (Goldman 1963, Yang, Koistinaho et al. 1989). The truth-table values for PVN, anterior pituitary, and adrenal gland with acute stress were set to 0.70. Stress maximally increases plasma CRF, ACTH, and cortisol, so the truth-table value for CRF, ACTH and cortisol with stress were set to 0.70 (Goldman 1963, Zimmermann and Critchlow 1967, Harbuz and Lightman 1989). NE levels have been found to moderately increase in response to stressful stimuli (Galvez, Mesches et al. 1996, Hatfield, Spanis et al. 1999). LC neuron activity has been found to moderately increase in response to stress (Abercrombie and Jacobs 1987, Buffalari and Grace 2007). Stress has also been shown to moderately increase tryptophan, 5HTP, 5HT and DA levels in many different brain regions (Thierry, Fekete et al. 1968, Abercrombie, Keefe et al. 1989, Kawahara, Yoshida et al. 1993, Summers, Kampshoff et al. 2003). We set the truth-table values for tryptophan, 5HTP, 5HT, NE and DA to 0.60. Acute stress moderately increases DR neuron firing rate in rodents, and VTA firing rate in cats, so the truth-table values for DR and VTA were set to 0.60 (Trulson and Preussler 1984, Bambico, Nguyen et al. 2009). Acute stress moderately increases glutamate levels, so the truth-table value for glutamate was set to 0.60 (Reznikov, Grillo et al. 2007). Acute stress moderately increases AVP and oxytocin levels, so the truth-table values for AVP and oxytocin were set to 0.60 (Hesketh, Jessop et al. 2005). The amygdala and hippocampus are moderately activated in response to stress while the PFC is moderately inhibited, so the truth-table values for the amygdala, hippocampus, and PFC were set to 0.60, 0.60 and 0.40, respectively (Sakanaka, Shibasaki et al. 1986, Van de Kar, Piechowski et al. 1991, Chen, Fenoglio et al. 2006, Alexander, Hillier et al. 2007, Qin, Hermans et al. 2009). Acute stress moderately elevates melatonin levels, so the truth-table value for melatonin was set to 0.60 (Lynch, Eng et al. 1973, Vollrath and Welker 1988). Foot-shock stress causes a moderate decrease in GABA in rats, so this truth-table value was set to 0.40 (Biggio, Corda et al. 1981). Acute immobilization-stress produces no change in galanin levels in the amygdala, so the truth-table value for galanin with stress was set to 0.50 (Khoshbouei, Cecchi et al. 2002).

With the adrenalectomy (ADX) input, the adrenal gland truth-table value was set to 0.30 (Iacobone, Albiger et al. 2008). ADX has been found to maximally decrease plasma cortisol levels, so the truth-table value for cortisol with ADX was set to 0.30 (Butler, Clarke et al. 1969). This results in a maximal rise in CRF and ACTH as well as a moderate rise in AVP, so the truth table

values for CRF and ACTH were set to 0.70 for AVP was set to 0.60 with adrenalectomy (Vernikos-Danellis 1965, Fink, Robinson et al. 1988, Unno, Wu et al. 1998, Iacobone, Albiger et al. 2008). Because subsequent PVN and pituitary-gland firing rates moderately increase with ADX, we set the truth-table values for PVN and pituitary gland to 0.60 (Kitay, Holub et al. 1959, Wynn, Harwood et al. 1985, Kasai and Yamashita 1988). Oxytocin levels were unaffected by adrenalectomy, so the truth table value for oxytocin with adrenalectomy was set to 0.50 (Fink, Robinson et al. 1988). The combination of ADX/Stress has been found to maximally increase ACTH levels in female rats, so the truth-table value for ACTH with ADX/Stress was set to 0.70 (Vernikos-Danellis 1965). The combination of ADX/Dex has been found to moderately decrease ACTH and AVP levels, so the truth-table values of ACTH and AVP with ADX/Dex were set to 0.40 (Fink, Robinson et al. 1988).

Exogenous ACTH projects to ACTH receptors (Kitay, Holub et al. 1959). Intramuscular injections of ACTH in horses leads to a moderate increase in cortisol levels after 2-4 hours, so the truth-table value for cortisol with exogenous ACTH was set to 0.60 (Thorn, Forsham et al. 1950, Larsson, Edqvist et al. 1979). ACTH has been shown to increase adrenal gland activity, so the truth-table value for adrenal gland with exogenous ACTH was set to 0.60 (Yang, Koistinaho et al. 1990).

Exogenous CRF projects to CRF1 and CRF2 receptors in the structure matrix (Merchenthaler 1984). Exogenous CRF administration in humans has been found to moderately increase plasma ACTH and cortisol levels (Hermus, Pieters et al. 1984). The truth-table values for ACTH and cortisol with exogenous CRF were both set to 0.60.

Lesions to the PVN, amygdala, hippocampus and PFC all result in maximal decreases in PVN, amygdala, hippocampus, and PFC, respectively (Chang, Tran et al. 1980). The truth-table values for PVN, amygdala, hippocampus, and PFC, with PVN lesion, amygdala lesion, hippocampus lesion, and PFC lesion, respectively, were all set to 0.30. PVN lesion maximally reduces CRF levels and moderately reduces oxytocin levels, so the truth-table values for CRF and oxytocin with PVN lesion were set to 0.30 and 0.40, respectively (Bruhn, Plotsky et al. 1984, Antoni, Fink et al. 1990). Basal ACTH levels have also been found to moderately decrease with a PVN lesion, so the truth-table value for ACTH was set to 0.40. PVN lesion has been found to maximally decrease melatonin levels, so the truth-table value for melatonin with PVN lesion was set to 0.30 (Klein, Smoot et al. 1983). Adrenal gland activity has been found to moderately

decrease with PVN lesion, so the truth-table value for adrenal gland was set to 0.40 (Makara, Stark et al. 1981).

The combination of PVN lesion and stress results in a moderate increase in CRF, ACTH, and cortisol (Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984, Makara 1992). The truth table values for these were therefore set to 0.60. Amygdala lesion and stress has been shown to lead to a moderate increase in CRF, ACTH, and cortisol, so the truth table values for these were also set to 0.60 (Sakanaka, Shibasaki et al. 1986, Van de Kar, Piechowski et al. 1991, Feldman, Conforti et al. 1994). However, lesions of the PFC and hippocampus combined with stress lead to maximal elevations of ACTH and cortisol (Jacobs, Wise et al. 1974, Herman, Schafer et al. 1989, Jacobson and Sapolsky 1991, Diorio, Viau et al. 1993, Herman, Cullinan et al. 1995). We set the truth-table values for ACTH and cortisol with PFC lesion/Stress and Hippocampus lesion/stress to 0.70.

The combination of PVN lesion and a 5HT1A receptor agonist prevented the rise in ACTH observed with the agonist by itself, so the truth-table value for ACTH with PVN lesion/Gepirone was set to 0.50 (Bluet Pajot, Mounier et al. 1995).

The Dexamethasone/CRF test is widely used in depression research to detect HPA axis dysfunction (Rush, Giles et al. 1996, Kunugi, Ida et al. 2006, Heim, Mletzko et al. 2008). CRF is injected after pretreatment with Dexamethasone (Kunugi, Ida et al. 2006). In normal control subjects, ACTH and cortisol secretion does not increase, but in stressed subjects, this test shows moderate increases in ACTH and cortisol secretion (Hohnloser, Von Werder et al. 1989, Kunugi, Ida et al. 2006, Heim, Mletzko et al. 2008). We therefore set the truth-table values for ACTH and cortisol with Dexamethasone/CRF to 0.50, and the truth-table values for ACTH and cortisol with Dexamethasone/CRF/stress to 0.60.

Acute restraint stress with acute SSRI has been found to moderately increase AVP levels, so the truth-table value for AVP with SSRI/stress was set to 0.60 (Hesketh, Jessop et al. 2005). Oxytocin and CRF levels moderately increase with SSRI/stress, so the truth-table values for oxytocin and CRF with SSRI/Stress were set to 0.60 (Hesketh, Jessop et al. 2005). The combination of SSRI/Stress has been found to produce a maximal increase in ACTH and cortisol, so the truth-table values for ACTH and cortisol were set to 0.70 with SSRI/Stress (Hesketh, Jessop et al. 2005). SSRI/Stress has been found to maximally increase NE levels, so the truth-table value for NE with SSRI/stress was set to 0.70 (Page and Abercrombie 1997).

The combination of an SSRI and a 5HT1AR antagonist (SSRI/WAY) has been found to

maximally increase 5HT levels, so the truth-table value for SSRI/WAY was set to 0.70 (Arborelius, Nomikos et al. 1996). The combination of an SSRI and WAY has been found to produce no change in DR firing rate from baseline, so the truth-table value for DR with SSRI/WAY was set to 0.50 (Arborelius, Nomikos et al. 1995, Hajos, Gartside et al. 1995).

Co-administration of an SSRI and Bupropion (SSRI/Bupropion) has been found by the Blier group to double DR firing rate and decrease LC firing rate by 60% (Ghanbari, El Mansari et al. 2010). The truth-table values for DR and LC with SSRI/Bupropion were set to 0.60 and 0.40, respectively. SSRI/Bupropion have been found to moderately increase 5HT, NE and DA levels, so the truth-table values for 5HT, NE and DA with acute SSRI/Bupropion were set to 0.60 (Li, Perry et al. 2002).

The Blier group found that the combination of an SSRI and Aripiprazole (SSRI/Aripiprazole) produces no significant change in the firing of DR or VTA neurons, but decreases LC neuron firing by 26%. (Chernoloz, El Mansari et al. 2009). The truth table values for DR, LC, and VTA with SSRI/Aripiprazole were set to 0.50, 0.40, and 0.50, respectively.

The Blier group found that the combination of an SSRI and Quetiapine (SSRI/Quetiapine) produces a 65% decrease in DR neuron firing and a 27% increase in LC neuron firing (Chernoloz, El Mansari et al. 2012). The truth table values for DR and LC with SSRI/Quetiapine were therefore set to 0.40 and 0.60, respectively.

The combination of Reboxetine and fearful stimuli (fearful faces) has been found to moderately increase amygdala activity in fMRI experiments (Onur, Walter et al. 2009). The truth-table value for amygdala with Reboxetine/Stress was set to 0.60. The combination of Reboxetine and stress in rodents has been found to produce no change in 5HT levels, maximally increases NE levels, and moderately increase DA levels (Page and Lucki 2002). The truth-table values for 5HT, NE and DA with Reboxetine/Stress were set to 0.50, 0.70, and 0.60, respectively.

B.8 MSS-MODEL TRUTH-TABLE JUSTIFICATION

The MSS-model includes the truth-table input/desired-output relationships derived from male organisms in the MS-model. All additional input/desired-output relationships are described here. The scale used to describe truth-table desired-outputs (where 0.30, 0.40, 0.50, 0.60, and 0.70 represent maximal decrease, moderate decrease, baseline, moderate increase, and maximal increase) is the same in both studies (Camacho, Vijitbenjaronk et al. 2018). The only exception in

the MSS-model is that he baseline for testosterone, estrogen, and progesterone was set to 0.60, 0.40, and 0.40, respectively, to reflect the difference in the levels of these hormones in males.

Binding of the SSRI to 5HTT leads to a doubling of extracellular 5HT in male rodents, so the target-output value for 5HT with acute SSRI was set to 0.60 (Invernizzi, Belli et al. 1992, Koch, Perry et al. 2002, Calcagno, Guzzetti et al. 2009). Because acute administration of SSRIs other than fluoxetine does not significantly change NE and DA levels in male rodents, the truth table values for these neurotransmitters were set to 0.50 (Bymaster, Zhang et al. 2002, Koch, Perry et al. 2002).

The increase in extracellular 5HT associated with acute SSRI administration has been associated with increased binding to the 5HT1A autoreceptor on DR neurons, decreasing the firing activity of these neurons in male rodents (Calcagno, Guzzetti et al. 2009). The Blier group and others have found that the DR neuron firing rate decreases by about 65% in male rodents with acute SSRI, so the truth-table value for this output was set to 0.40 (de Montigny, Chaput et al. 1990, Czachura and Rasmussen 2000, Chernoloz, El Mansari et al. 2012). The Blier group found that acute SSRI administration decreases the firing rate of LC neurons by 45% and decreases the firing rate of VTA neurons by 41% in male rodents, so the truth table values for the LC and VTA firing rates with acute SSRI were also set to 0.40 (Chernoloz, El Mansari et al. 2009, Dremencov, El Mansari et al. 2009, Chernoloz, El Mansari et al. 2012). fMRI studies indicate that amygdala activity decreases moderately in both males and females, while cortical activity does not change with acute SSRI administration in males (Mayberg, Brannan et al. 2000, Kennedy, Evans et al. 2001, Takahashi, Yahata et al. 2005, Murphy, Norbury et al. 2009). The Murphy lab found that amygdala activity decreases moderately in response to neutral faces with acute SSRI in both male and female subjects, and the Mayberg lab found that PFC activity moderately increases after 6-weeks of SSRI treatment but not after acute (1-week) SSRI treatment in male subjects. The truth table value for the amygdala with acute SSRI were set to 0.40 and the truth table value for PFC was set to 0.50.

Acute SSRI administration has been found to stimulate the rodent HPA axis by increasing CRF, ACTH, and cortisol levels while also increasing PVN activity in male rodents (Jensen, Jessop et al. 1999, Wieczorek, Schulz et al. 2001, Hesketh, Jessop et al. 2005). Specifically, 30 minutes of subcutaneous cannula citalopram administration moderately increases ACTH levels (Jensen, Jessop et al. 1999). This lab also found that PVN activity increases moderately as measured by the

increase in c-fos immunoreactive cells in the PVN with acute SSRI. The same lab did not find a significant difference in CRF mRNA with acute citalopram treatment; however, another lab found that acute citalopram moderately increases CRF levels in male rodents (Moncek, Duncko et al. 2003). The truth table value for ACTH with acute SSRI was set to 0.60 in the MSS-model. The truth table value for CRF with acute SSRI was set to 0.60. Systemic injection citalopram increases corticosterone response maximally in males so the cortisol level with SSRI was set to 0.70 (Goel and Bale 2010, Goel, Plyler et al. 2011, Goel, Workman et al. 2014). Oxytocin levels have been found to moderately increase with acute SSRI, while arginine-vasopressin (AVP) levels have been found to stay the same in male rodents (Hesketh, Jessop et al. 2005). We set the oxytocin target to 0.60 and the AVP target to 0.50 with acute SSRI for males. Acute fluoxetine injection moderately increases galanin mRNA levels in male rodents, so the truth-table value for galanin with acute SSRI was set to 0.60 for males (Kuteeva, Wardi et al. 2008). Acute SSRI administration in male humans had no effect on testosterone levels, so the truth-table value for testosterone with acute SSRI for males was set to 0.60 (Schlosser, Wetzel et al. 2000).

The Blier group found that acute administration of Nomifensine increases DR neuron activity by 50%, decreases VTA neuron activity by 39%, and decreases LC neuron activity by 71% in male rodents (Katz, Guiard et al. 2010). The truth-table values for the acute effect of Nomifensine on DR, LC and VTA neurons were set to 0.60, 0.40, and 0.40, respectively. The Masana study also found that acute Nomifensine maximally increases DA levels in males. The Carboni lab found that acute Nomifensine maximally increases DA levels in male rodents (Carboni, Imperato et al. 1989). The Butcher lab found a moderate increase in DA levels with acute Nomifensine in male rats (Butcher, Fairbrother et al. 1988). The truth-table value for DA with acute Nomifensine was set to 0.60.

Reboxetine is a selective NET blocker (Hajos, Fleishaker et al. 2004). The Blier group found that acute Reboxetine administration decreases LC firing rate by 68% without affecting DR firing rate in male rodents (Szabo and Blier 2001). They also found that acute Reboxetine administration decreases VTA neuron firing rate by 31% in male rodents (Katz, Guiard et al. 2010). The truth-table values for acute Reboxetine for DR, LC, and VTA were therefore set to 0.50, 0.40, and 0.40, respectively. Acute Reboxetine administration moderately increases NE and DA levels while producing no change in 5HT levels in male rodents, corresponding to values of 0.60, 0.60, and 0.50 in the truth table for these neurotransmitters, respectively (Page and Lucki 2002). One

fMRI study in both male and female humans shows that acute Reboxetine administration moderately decreases amygdala response to neutral stimuli, so the truth-table value for the amygdala with acute Reboxetine was set to 0.40 (Onur, Walter et al. 2009). Acute Reboxetine administration in male humans has been found to moderately increase ACTH levels in two studies using male volunteers, so the truth-table value for ACTH with acute Reboxetine was set to 0.60. Acute Reboxetine administration has also been shown to moderately increase cortisol levels in two different studies using male human volunteers, so the truth-table value for cortisol with acute Reboxetine was set to 0.60 (Hennig, Lange et al. 2000, Schule, Baghai et al. 2004).

Trazodone blocks 5HTT and interacts with multiple receptors of the monoaminergic system (Stahl 2009, Stahl 2009). The Blier lab found that acute Trazodone administration decreases DR neuron firing by 65%, increases LC neuron firing by 25%, and does not alter VTA neuron firing in male rodents (Ghanbari, El Mansari et al. 2010, Ghanbari, El Mansari et al. 2012). We set the target output values for DR, LC, and VTA with acute Trazodone to 0.40, 0.60, and 0.50, respectively. Acute Trazodone administration has been found to moderately increase 5HT levels without changing NE levels in male rodents, so the truth-table values for these were set to 0.60 and 0.50, respectively (Rowbotham, Jones et al. 1984, Pazzagli, Giovannini et al. 1999).

Asenapine is an antipsychotic drug that interacts with multiple receptors of the monoaminergic neurotransmitter system (Franberg, Wiker et al. 2008, Ghanbari, El Mansari et al. 2009). The Blier group found that acute Asenapine administration decreases DR neuron firing by about 30% without affecting the firing rates of the LC or VTA in male rodents (Oosterhof, El Mansari et al. 2015). We set the truth table values for DR, LC, and VTA to 0.40, 0.50, and 0.50, respectively. Acute Asenapine administration in male rats has been found to moderately increase 5HT, NE, and DA levels (Franberg, Marcus et al. 2009). The truth table outputs for 5HT, NE, and DA with acute Asenapine were all set to 0.60.

Aripiprazole is an antipsychotic drug that interacts strongly with DA and 5HT receptors (Shapiro, Renock et al. 2003). The Blier group found that acute Aripiprazole administration increases DR neuron firing rate by 48%, without affecting the firing rates of LC or VTA neurons in male rodents (Chernoloz, El Mansari et al. 2009). The truth-table values for the DR, LC and VTA were set to 0.60, 0.50 and 0.50, respectively. Acute Aripiprazole administration has been found to moderately increase DA levels without affecting 5HT, NE, or cortisol levels in male rodents (Li, Ichikawa et al. 2004, Zocchi, Fabbri et al. 2005, Assie, Carilla-Durand et al. 2008).

The truth-table values for 5HT, NE, DA, and cortisol were set to 0.50, 0.50, 0.60, and 0.50 with acute Aripiprazole, respectively.

Bupropion is an atypical antidepressant that blocks NET and DAT (Cooper, Wang et al. 1994, Stahl, Pradko et al. 2004). The Blier group found that acute Bupropion administration moderately increases DR neuron firing rate, moderately decreases LC neuron firing rate, and does not change VTA neuron firing rate in male rodents (El Mansari, Ghanbari et al. 2008). The truth-table values for the DR, LC and VTA were set to 0.60, 0.40 and 0.50, respectively, for males with acute Bupropion administration. Acute Bupropion administration has been found to moderately increase DA and NE levels without affecting 5HT levels in male rodents (Piacentini, Clinckers et al. 2003). The truth-table values for 5HT, NE, DA were set to 0.50, 0.60, and 0.60 with acute Bupropion in the MSS-model.

Quetiapine is an antipsychotic drug with multiple receptor and transporter affinities, including the dopamine D2 receptor, the 5HT2A receptor, and the α-1 receptor (DeVane and Nemeroff 2001, Jensen, Rodriguiz et al. 2008). The Blier group found that acute Quetiapine administration decreases the DR neuron firing rate by 43% and increases the LC neuron firing rate by 40% in male rodents (Chernoloz, El Mansari et al. 2012). The truth-table values for the DR and LC with acute Quetiapine were set to 0.40 and 0.60, respectively. Another group found that acute Quetiapine moderately increases VTA firing rate in males, so the truth-table value for the VTA with acute Quetiapine was set to 0.60 for males (Werkman, Olijslagers et al. 2004). Denys et al found that acute Quetiapine moderately increases 5HT and DA levels in the PFC, while Silverstone et al found that acute Quetiapine has no effect on 5HT levels in the PFC, but moderately increases NE and DA levels (Denys, Klompmakers et al. 2004, Silverstone, Lalies et al. 2012). Both of these studies were in male rodents. Because the Denys et al study examined multiple brain regions and also found a moderate increase in 5HT levels in the dorsal striatum with acute Quetiapine, the truth table value for DA was set to 0.60. The truth table values for 5HT and NE with acute Quetiapine were also set to 0.60.

Pramipexole (PPX) is a D2, D3, and D4 receptor agonist (Mierau, Schneider et al. 1995). The Blier group found that acute PPX administration does not change DR neuron firing rate, decreases LC neuron firing rate by 33%, and decreases VTA neuron firing rate by 40% in male rodents (Chernoloz, El Mansari et al. 2009). The truth-table values for the DR, LC and VTA were set to 0.50, 0.40 and 0.40, respectively, with acute PPX administration, for males.

GBR-12909 (GBR) is a DA transporter blocker (TOCRIS , Andersen 1989, Singh 2000). The Blier group found that acute GBR administration does not change DR or LC neuron firing rate but decreases VTA neuron firing rate by 26% in male rodents (Katz, Guiard et al. 2010). Another group also found a moderate decrease in VTA neuron firing rate with acute GBR in male rodents (Choong and Shen 2004). The truth-table values for the DR, LC and VTA were set to 0.50, 0.50 and 0.40, respectively, with acute GBR administration. Three labs have found moderate increases in DA levels with acute GBR in male rodents, so the truth-table value of DA with acute GBR was set to 0.60 (Rothman, Mele et al. 1991, Choong and Shen 2004, Masana, Bortolozzi et al. 2011).

Clozapine is an antipsychotic drug that targets many monoaminergic receptors (Meltzer 1994). Acute administration of Clozapine has been found to moderately decrease the firing rate of DR neurons, moderately increase the firing rate of LC neurons, moderately increase the firing rate of VTA neurons, and moderately increase the firing rate of PFC neurons in male subjects (Souto, Monti et al. 1979, Sprouse, Reynolds et al. 1999, Chen and Yang 2002, Gao 2007). Another group found that acute Clozapine completely inhibits DR firing activity in male rodents; however, the dose that was used was much higher than the standard rodent dose (Gallager and Aghajanian 1976). The truth-table values for DR, LC, VTA, and PFC were set to 0.40, 0.60, 0.60, and 0.60, respectively. Acute Clozapine administration has been found to maximally increase NE levels and moderately increase DA levels in male rodents (Zocchi, Fabbri et al. 2005). Another group also found that Clozapine moderately increases DA levels in male rodents (Masana, Bortolozzi et al. 2011). One study found that Clozapine moderately increases cortisol levels in male humans, so the truth table value for NE was set to 0.70 and the truth table values for DA and cortisol were set to 0.60 (Lee, Woo et al. 2001). One group has found that Clozapine decreases 5HT in the nucleus accumbens, while another found that Clozapine increases 5HT in the nucleus accumbens and the PFC in male rodents (Ferre and Artigas 1995, Ichikawa, Kuroki et al. 1998). Because these two groups found opposing effects of Clozapine on 5HT, and a third group found that 5HT does not change in the PFC with acute Clozapine, we used a truth-table value of 0.50 for 5HT with acute Clozapine (Zocchi, Fabbri et al. 2005).

Ketamine is an NMDA receptor antagonist (Hall and Murdoch 1990). The Blier group found that acute Ketamine administration does not change DR or VTA neuron firing rate but increases LC neuron firing rate by 23% in male rodents (El Iskandrani, Oosterhof et al. 2015). The truth-table values for the DR, LC and VTA were set to 0.50, 0.60, and 0.50, respectively, with

acute Ketamine administration. One group found that Ketamine moderately increases PFC neuron activity and moderately increases extracellular glutamate while another group found that Ketamine moderately increases anterior cingulate glutamate, so the truth-table value for the PFC and glutamate were set to 0.60 (Razoux, Garcia et al. 2007, Stone, Dietrich et al. 2012, Pehrson and Sanchez 2014, Bjorkholm, Franberg et al. 2015). These studies were done in male rodents and humans. One study found that Ketamine moderately increases PFC 5HT levels in male rodents, so the truth table value for 5HT was set to 0.60 with acute Ketamine for males (Nishitani, Nagayasu et al. 2014). Two groups found that Ketamine has no effect on GABA levels in male rodents, so the truth table value for GABA was set to 0.50 with acute Ketamine for males (Lindefors, Barati et al. 1997, Stone, Dietrich et al. 2012). One lab found that acute Ketamine had no effect on male rabbit whole brain NE or NE levels in any of the brain areas examined, so the truth table value for NE with acute Ketamine was set to 0.50. The same lab also found that DA levels did not change in male rabbit whole brain with Ketamine, but did find a moderate increase in thalamus and hypothalamus DA (Glisson, el-Etr et al. 1976). Another group found that acute Ketamine moderately increases DA levels in rat PFC (Lindefors, Barati et al. 1997). Because whole brain neurotransmitter level change is the standard criterion for the truth table, the truth-table value for DA with Ketamine was set to 0.50.

Reserpine depletes monoamines by inhibiting the activity of the vesicular monoamine transporter 2 (VMAT2), which traffics monoamines to the cell membrane for extracellular release (Scherman and Henry 1984, Rudnick, Steiner-Mordoch et al. 1990). Because VMAT2 is not an element in our model, Reserpine sends inhibitory projections directly to 5HT, NE and DA directly. One group found that Reserpine moderately increases DR activity, then suppresses DR activity after about 30 minutes in male rodents (Baraban, Wang et al. 1978, Baraban and Aghajanian 1980). Because we are interested in the immediate, acute effect of Reserpine, we set the truth-table value for DR with acute Reserpine to 0.60.

Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor (SNRI) (Roseboom and Kalin 2000). The Blier group found that Venlafaxine decreases DR firing rate by 47% and decreases LC firing rate by 21% in male rodents, so the truth-table values for DR and LC were both set to 0.40 (Gartside, Umbers et al. 1997). Because acute Venlafaxine administration moderately increases the firing activity of the PFC in a c-fos study with male rodents, we set the truth-table value for PFC with Venlafaxine to 0.60 (Higashino, Ago et al. 2014). Higashino et al

found that acute Venlafaxine administration moderately increases 5HT in the PFC, moderately increases NE in the PFC, and maximally increases DA in the PFC and Beyer et al found that acute Venlafaxine has no effect on forebrain 5HT levels but maximally increases forebrain NE levels (Beyer, Boikess et al. 2002, Higashino, Ago et al. 2014). Both of these studies were in male rodents. The truth-table value for 5HT was set to 0.60 in males to reflect a moderate increase in 5HT due to the observation by Higashino et al that 5HT increases in the PFC with Venlafaxine, and the fact that Venlafaxine is a 5HTT blocker, which are known to elevate 5HT (El Mansari, Sanchez et al. 2005). The truth-table values for NE and DA were both set to 0.70 in males to reflect the maximal increases in the levels of these neurotransmitters with acute Venlafaxine observed by the Higashino and Beyer groups.

Desipramine is a tricyclic antidepressant with strong affinity for NET and weaker affinity for the 5HTT and DAT as well as various monoaminergic receptor targets (Berti and Shore 1967). DR firing was found to moderately decrease with acute Desipramine in male rodents, so the truth-table value for DR was set to 0.40 with acute Desipramine (Gartside, Umbers et al. 1997). Acute Desipramine also moderately decreases LC neuron activity in male rodents, so the truth-table value for LC was set to 0.40 (Scuvee-Moreau and Dresse 1979). Acute administration of Desipramine was found by Beyer et al to maximally increase NE levels without changing 5HT levels, and Kreiss et al also found that Desipramine has no effect on 5HT levels (Kreiss and Lucki 1995, Beyer, Boikess et al. 2002). Both of these studies were in male rodents. Another group found no change in 5HT levels with acute Desipramine in male rodents, but found a maximal increase in NE levels and a moderate increase in DA levels (Higashino, Ago et al. 2014). The truth-table value for 5HT was set to 0.50, for NE was set to 0.70, and for DA was set to 0.60. Acute Desipramine was found to have no effect on PFC activity in male rodents, so this truth-table value was set to 0.50 (Higashino, Ago et al. 2014). Desipramine injection in both male and female humans moderately increases blood cortisol levels after 30 minutes, so the truth-table value for cortisol with Desipramine was set to 0.60 (Asnis, Halbreich et al. 1985). Desipramine moderately increases ACTH levels in males so the truth-table value for ACTH was set to 0.60 with acute Desipramine (Kuhn and Francis 1997).

CP-96345 (CP) is a neurokinin-1 receptor antagonist (Fong, Yu et al. 1992). The Blier group found that acute administration of CP in male rodents increases the firing rate of DR neurons by 46% but does not affect the firing rate of LC neurons, so the truth-table values for DR and LC

were set to 0.60 and 0.50 for the DR and LC with acute CP, respectively (Conley, Cumberbatch et al. 2002, Haddjeri and Blier 2008). One group found that NK1 receptor antagonists moderately increase VTA firing rate in male rodents, so the truth-table value for VTA with acute CP was set to 0.60. The same group also found that NK1 receptor antagonists have no effect on 5HT levels in male rodents, so the 5HT value with acute CP was set to 0.50 (Lejeune, Gobert et al. 2002). Another group found that acute CP has no effect on NE levels, but moderately increases DA levels in the PFC of male gerbils (Renoldi and Invernizzi 2006). DA levels moderately increase in male rodents with acute NK1 receptor antagonists (Lejeune, Gobert et al. 2002). The truth table value for NE was set to 0.50 and for DA was set to 0.60 with acute CP. The combination of NK1 antagonists and stress leads to no change in NE or DA levels in male rodents (Renoldi and Invernizzi 2006). The truth-table values for NE and DA with CP/Stress were set to 0.50.

Gepirone is a 5HT1A receptor agonist (Blier and Ward 2003). The Blier group and others have found that acute administration of 5HT1A agonists maximally decrease DR neuron firing rate in male rodents, so the truth-table value of DR with Gepirone was set to 0.30 (VanderMaelen, Matheson et al. 1986, Blier and de Montigny 1987, Blier and de Montigny 1990). 5HT1A receptor agonists have been found to maximally decrease 5HT levels in male rodents by multiple groups, so the truth table value for 5HT with acute Gepirone was set to 0.30 (Rutter, Gundlah et al. 1994, Dawson, Nguyen et al. 2002). 5HT1A receptor agonists have also been found to moderately increase CRF, ACTH, and cortisol release in male rodents, so the truth-table values for CRF, ACTH, and cortisol with acute Gepirone were set to 0.60 (Pan and Gilbert 1992, Matheson, Knowles et al. 1997). When males are castrated, their cortisol response to 5HT1A receptor agonists reach maximal levels, so the cortisol level for castrated males with gepirone was set to 0.70 (Matsuda, Nakano et al. 1991). The combination of Gepirone and stress moderately increases cortisol levels in male rodents, so the cortisol level in the truth-table with acute Gepirone/stress was set to 0.60 (Matheson, Knowles et al. 1997). The combination of Gepirone/Dexamethasone moderately decreases cortisol levels in male rodents, so the cortisol level in the truth-table with acute Gepirone/Dexamethasone was set to 0.40 (Matheson, Knowles et al. 1997).

Org34850 (Org) is a glucocorticoid receptor antagonist (Reynolds, Saunders et al. 2015). Acute Org administration by itself has been found to have no effect on cortisol, 5HT, or DA levels in male rodents, so the truth-table values for cortisol, 5HT, and DA with acute Org were set to 0.50 (Spiga, Harrison et al. 2007, Spiga, Harrison et al. 2008). Acute Org/Stress was also found by this

group to have no effect on cortisol levels in male rodents, so the truth-table value for cortisol with acute Org/Stress was set to 0.50.

Oxytocin is an input that projects to model oxytocin receptors (Gimpl and Fahrenholz 2001). Oxytocin administration to male rats has been shown to double DA levels, so the truth-table value for DA was set to 0.60 (Melis, Melis et al. 2007). Oxytocin by itself as well as Oxytocin/Stress has no effect on PVN CRF mRNA in male rats, so the CRF value with Oxytocin and with Oxytocin/Stress was set to 0.50 (Bulbul, Babygirija et al. 2011). Oxytocin has been found to moderately decrease amygdala response to fearful stimuli (faces and scenery) in human males, so the truth-table value for amygdala with Oxytocin/Stress was set to 0.40 (Kirsch, Esslinger et al. 2005). One study in rats from 1984 found that Oxytocin does not have a significant effect on ACTH levels, however, because several other groups since 1984 have found that Oxytocin moderately decreases ACTH in both male and female subjects, the truth-table values for ACTH with Oxytocin were set to 0.40 (Gibbs, Vale et al. 1984, Chiodera and Coiro 1987, Parker, Buckmaster et al. 2005). It has also been found that Oxytocin moderately decreases cortisol levels in male humans, so the truth-table value for cortisol with Oxytocin was set to 0.40 (Legros, Chiodera et al. 1984).

Dexamethasone is a corticosteroid with significant in vivo affinity for glucocorticoid receptors but not mineralocorticoid receptors (Bamberger, Bamberger et al. 1995, Reul, Gesing et al. 2000, Pariante and Miller 2001). One group found that Dexamethasone maximally decreases cortisol levels in males, so the truth-table value for cortisol with Dexamethasone was set to 0.30 (Heuser, Gotthardt et al. 1994, Rush, Giles et al. 1996). Dexamethasone maximally suppresses PVN CRF mRNA in male rodents, so the truth-table value for CRF with Dexamethasone was set to 0.30 (Kovacs and Mezey 1987). Acute Dexamethasone administration moderately decreases ACTH levels in male humans, so the truth-table value for ACTH with Dexamethasone was set to 0.40 (Hohnloser, Von Werder et al. 1989). Acute Dexamethasone moderately decreases AVP mRNA in the PVN of male rodents, so the truth-table value for AVP with Dexamethasone was set to 0.40 (Kovacs and Makara 1988). C-fos mRNA responses in the PVN and pituitary gland were found to be moderately decreased with acute Dexamethasone in male rodents, so the truth-table values for the PVN and pituitary gland were set to 0.40 (Karssen, Meijer et al. 2005). Dexamethasone administration has been shown to moderately increase the levels of 5HT precursors and 5HT in male rodents, so the truth-table values for Trp, 5HTP, and 5HT were set to

0.60 with Dexamethasone (Tsubota, Adachi et al. 1999, Clark, Flick et al. 2008). Dexamethasone has also been found to moderately increase the levels of extracellular DA in male rodents but moderately decrease extracellular NE in both male and female humans, so the truth-table values for DA and NE were set to 0.60 and 0.40, respectively (Stene, Panagiotis et al. 1980, Tsubota, Adachi et al. 1999). Dexamethasone administration in male rodents has been found to decrease testosterone levels, so the truth-table value for testosterone with Dexamethasone was set to 0.50 (Saez, Morera et al. 1977).

WAY-100635 (WAY) is a 5HT1A receptor antagonist (Fletcher, Forster et al. 1996). Administration of WAY has been shown to reverse the inhibitory effects of 5HT1A receptor agonists on DR firing rate in both male and female rodents, so the truth-table value for DR with WAY/Gepirone was set to 0.50 (Evrard, Laporte et al. 1999). WAY/Gepirone together has also been shown to prevent the rise in ACTH observed with Gepirone in male rodents, so the truth-table value for ACTH with WAY/Gepirone was set to 0.50 (Fletcher, Forster et al. 1996). 5HT1AR antagonists by themselves moderately increase extracellular 5HT in male rodents, so the truth-table value for 5HT with WAY was set to 0.60 (Arborelius, Nomikos et al. 1996).

Monoamine Oxidase Inhibitors (MAOI) block the activity of monoamine oxidase, which is an enzyme that breaks down monoamines (Stein 1960, Remick and Froese 1990). The Blier group found that acute MAOI administration moderately decreases DR and LC neuron firing without affecting VTA neuron firing in male rodents, so the truth-table values for DR and LC were set to 0.40 and the truth table value for VTA was set to 0.50 with MAOI for males (Blier and de Montigny 1985, Chenu, El Mansari et al. 2009). Acute MAOI administration has been shown to produce maximal increases in all three of the monoamines in male rodents, so the truth-table values for 5HT, NE and DA were set to 0.70 (Butcher, Fairbrother et al. 1990, Celada and Artigas 1993, Kitaichi, Inoue et al. 2006).

M-617 inhibits galR1 receptors (Sevcik, Finta et al. 1993, Larm, Shen et al. 2003, Wang, Li et al. 2016). Acute M617 administration moderately decreases DR and LC firing rate and moderately decreases 5HT and NE levels in male rodents (Jacobs, Wise et al. 1974, Azmitia and Segal 1978, Seutin, Verbanck et al. 1989, Sevcik, Finta et al. 1993, Yoshitake, Reenila et al. 2003, Hawes, Brunzell et al. 2005, Mazarati, Baldwin et al. 2005). We therefore set the truth-table values for DR, LC, 5HT, and NE to 0.40. It has also been found that M617 administration produces moderate increases in the activity of the amygdala and PVN as measured by increases in c-fos

expression in these regions of male rodents, so the truth-table values for these regions were set to 0.60 (Blackshear, Yamamoto et al. 2007).

CRF1 receptor antagonists block the CRF1 receptor (Holsboer and Ising 2008). Specifically, multiple labs have found that CRF1R antagonists moderately decrease ACTH and cortisol release in both male and female subjects, so the truth-table values for ACTH and cortisol with CRF1R antagonist were set to 0.40 (Broadbear, Winger et al. 2004, Jutkiewicz, Wood et al. 2005, Ising and Holsboer 2007). Acute administration of CRF1R antagonist/Stress moderately increases ACTH and cortisol in male rodents, so the truth-table values for ACTH and cortisol for CRF1R antagonist/stress was set to 0.60 for males (Deak, Nguyen et al. 1999, Jutkiewicz, Wood et al. 2005).

Haloperidol is a dopamine D2 receptor antagonist (Schotte, Janssen et al. 1993). Subcutaneous haloperidol administration in rats produces no change in PFC NE or DA levels in male rodents, so the truth table values for NE and DA with acute Haloperidol were set to 0.50 (Li, Perry et al. 1998). The combination of Haloperidol and Bupropion produces no change in the firing rate of VTA neurons in male rodents, so the truth-table value for VTA with Haloperidol/Bupropion was set to 0.50 (Cooper, Wang et al. 1994).

Olanzapine is dopamine D2 receptor antagonist and 5HT2A receptor antagonist (Pilowsky, Busatto et al. 1996). Subcutaneous Olanzapine administration in male rats moderately increases PFC NE and DA levels, so the truth table values for NE and DA with acute Olanzapine were set to 0.60 (Li, Perry et al. 1998).

Clonidine is an α-2 receptor agonist (Unnerstall, Kopajtic et al. 1984). Administration of Clonidine has been found to moderately decrease LC neuron firing in male rodents, and moderately decrease NE levels in both male and female humans (Svensson, Bunney et al. 1975, Veith, Best et al. 1984, Jacobs 1986). The truth-table value for LC with acute Clonidine was set to 0.40. The truth-table value for NE with acute Clonidine was set to 0.40.

Yohimbine is an α-2 receptor antagonist (Perry and U'Prichard 1981). Yohimbine administration in male rats moderately elevates NE levels in the amygdala, so the truth-table value for NE with acute Yohimbine was set to 0.60 (Khoshbouei, Cecchi et al. 2002). The combination of Yohimbine and Stress maximally increases NE levels in the amygdala of male rats, so the truth-table value for NE with acute Yohimbine/Stress was set to 0.70 (Khoshbouei, Cecchi et al. 2002). The combination of Yohimbine/Stress was also found to moderately elevate galanin levels in male

rats, so the truth-table value for galanin with Yohimbine/Stress was set to 0.60 (Khoshbouei, Cecchi et al. 2002). The combination of an alpha-2 receptor antagonist and CRF produces moderate increases in ACTH and cortisol in both males and females, so the truth-table values for ACTH and cortisol with Yoh/CRF were set to 0.60 (Kizildere, Gluck et al. 2003).

Administration of an alpha-1 agonist in male subjects moderately increases AVP levels, so the truth-table value for AVP with alpha-1 agonist was set to 0.60 (Armstrong, Gallagher et al. 1986).

The Blier group did a series of experiments in male rodents where they lesioned one of the monoaminergic nuclei, then observed the change in the firing activity of the other two monoaminergic nuclei to determine how they influence one another. The results of these experiments are included in the truth table and described in detail in the supplement to the MS-model study (Camacho, Vijitbenjaronk et al. 2018).

The stress input sends an excitatory projection to the PVN (Sapolsky 2000, Gold and Chrousos 2002, de Kloet, Joels et al. 2005). Stress leads to maximal elevation of PVN activity as measured by induction of c-fos mRNA expression in male rats (Cullinan, Herman et al. 1995). Stress also leads to maximal increases in the activity of the adrenal gland in male rodents as measured by maximal blood flow increases after acute stress and c-fos induction (Goldman 1963, Yang, Koistinaho et al. 1989). The truth-table values for PVN and adrenal gland were set to 0.70 with stress. Stress moderately increases plasma CRF, ACTH, and cortisol in male subjects, so the truth-table values for CRF, ACTH and cortisol with stress were set to 0.60 (Kitay 1961, Viau, Bingham et al. 2005, Iwasaki-Sekino, Mano-Otagiri et al. 2009) (Goldman 1963, Zimmermann and Critchlow 1967, Harbuz and Lightman 1989, Rivier 1993). Castrated males have maximal increases in CRF, ACTH, cortisol, and AVP in response to stress, so the truth-table values for CRF, ACTH, cortisol, and AVP were all set to 0.70 for castrated males (Seale, Wood et al. 2004). When testosterone is administered to castrated males, their stress-induced increases in ACTH and cortisol return to moderate levels, so the truth-table values for ACTH and cortisol for stressed, castrated and testosterone-infused males were set to 0.60 (Handa, Nunley et al. 1994, Viau and Meaney 1996). NE levels have been found to moderately increase in response to stressful stimuli in both male and female subjects, so the truth-table value for NE with stress was set to 0.60 (Galvez, Mesches et al. 1996, Hatfield, Spanis et al. 1999). LC neuron activity in both male and female subjects has been found to moderately increase in response to stress (Abercrombie and

Jacobs 1987, Buffalari and Grace 2007). Stress has also been shown to moderately increase tryptophan, 5HTP, 5HT and DA levels in many different brain regions of male subjects (Thierry, Fekete et al. 1968, Abercrombie, Keefe et al. 1989, Kawahara, Yoshida et al. 1993, Summers, Kampshoff et al. 2003). We set the truth-table values for tryptophan, 5HTP, 5HT, NE, LC and DA to 0.60. Acute stress moderately increases DR neuron firing rate in male rodents, and VTA firing rate in both male and female cats, so the truth-table values for DR and VTA were set to 0.60 (Trulson and Preussler 1984, Bambico, Nguyen et al. 2009). Acute stress also moderately increase 5HT and DA levels in castrated males, so the truth-table values for 5HT and DA with acute stress were set to 0.60 for castrated males (Doge 1993). Acute stress moderately increases glutamate levels in male rodents, so the truth-table value for glutamate was set to 0.60 (Reznikov, Grillo et al. 2007). Acute stress moderately increases AVP and oxytocin levels in male rodents, so the truth-table values for AVP and oxytocin were set to 0.60 (Hesketh, Jessop et al. 2005). The amygdala and hippocampus are moderately activated in response to stress in males while the PFC is moderately inhibited in both males and females, so the truth-table values for the amygdala, hippocampus, and PFC were set to 0.60, 0.60 and 0.40, respectively (Sakanaka, Shibasaki et al. 1986, Van de Kar, Piechowski et al. 1991, Chen, Fenoglio et al. 2006, Alexander, Hillier et al. 2007, Qin, Hermans et al. 2009). Acute stress moderately elevates melatonin levels in male rodents, so the truth-table value for melatonin was set to 0.60 (Lynch, Eng et al. 1973, Vollrath and Welker 1988). Foot-shock stress causes a moderate decrease in GABA in both male and female rats, so this truth-table value was set to 0.40 (Biggio, Corda et al. 1981). Acute immobilization-stress produces no change in galanin levels in the amygdala of male rodents, so the truth-table value for galanin with stress was set to 0.50 (Khoshbouei, Cecchi et al. 2002). Surgical stress was found to moderately decrease testosterone levels in human males, so testosterone was set to 0.50 with stress (Aono, Kurachi et al. 1976). Stress moderately increases 5HT levels in males, so the truth-table value for 5HT was set to 0.60 (Mitsushima, Yamada et al. 2006, Lanfumey, Mongeau et al. 2008, Jacobson-Pick, Audet et al. 2013). Adding progesterone to stress in males moderately increases plasma progesterone levels and prevents the rise in cortisol associated with stress (Childs, Van Dam et al. 2010). The truth-table value for progesterone and cortisol for Progesterone/Stress were set to 0.50.

With the adrenalectomy (ADX) input, the adrenal gland truth-table value was set to 0.30 (Iacobone, Albiger et al. 2008). ADX moderately increases testis activity in male rodents, so the

truth-table value for testis with ADX was set to 0.60 (Desjardins and Ewing 1971). However, testosterone levels have been found to stay the same with ADX in intact male rats (Saez, Morera et al. 1977). ADX results in a maximal rise in CRF and ACTH as well as a moderate rise in AVP in both male and female subjects, so the truth table values for CRF and ACTH were set to 0.70 for AVP was set to 0.60 with adrenalectomy (Vernikos-Danellis 1965, Fink, Robinson et al. 1988, Unno, Wu et al. 1998, Iacobone, Albiger et al. 2008). Because PVN and pituitary gland firing-rates moderately increase with ADX in male subjects, we set the truth-table values for PVN and pituitary gland to 0.60 (Kitay, Holub et al. 1959, Wynn, Harwood et al. 1985, Kasai and Yamashita 1988). ADX/Dex has been found to produce no change in testosterone levels in male rats, so the truth-table value for testosterone with ADX/Dex was set to 0.60 (Saez, Morera et al. 1977). ADX produces no change in serum LH levels in intact male rats, so the truth-table value for LH with ADX was set to 0.50 (Mann, Free et al. 1987). ADX in castrated male rats does not change LH and FSH levels, so the truth-table values for LH and FSH with ADX were set to 0.50 for castrated males (Schwartz and Justo 1977). The combination of ADX/Corticosterone was found to have no change on testis activity, but a decrease in testosterone level (Desjardins and Ewing 1971). The truth-table values for testis and testosterone were both set to 0.50 with corticosterone/ADX. The combinations of ADX/hCG, ADX/hCG/Dex, and ADX/ACTH/hCG all resulted in a moderate increase in testosterone levels in intact male rats, so testosterone was set to 0.70 for all of these combinations (Saez, Morera et al. 1977).

Exogenous ACTH projects to ACTH receptors, and raises ACTH levels, so the truth-table value for ACTH was set to 0.60 (Kitay, Holub et al. 1959). Intramuscular injections of ACTH in male horses leads to a moderate increase in cortisol levels after 2-4 hours, so the truth-table value for cortisol with exogenous ACTH was set to 0.60 (Thorn, Forsham et al. 1950, Larsson, Edqvist et al. 1979). ACTH has been shown to increase adrenal gland activity in male rats, so the truth-table value for adrenal gland with exogenous ACTH was set to 0.60 (Yang, Koistinaho et al. 1990). Exogenous ACTH for three days produces no change in LH levels but moderately decreases testosterone levels in intact male rats, so the truth-table values for LH and testosterone with exogenous ACTH were both set to 0.50 (Saez, Morera et al. 1977, Mann, Free et al. 1987). Exogenous ACTH in intact male rats has been found to decrease testis size, so the truth-table value for testis was set to 0.40 with Exogenous ACTH (Baker, Schairer et al. 1950). Exogenous ACTH has also been found to increase progesterone levels in intact male rats, so the truth-table value for

progesterone with exogenous ACTH was set to 0.50 (Mann, Free et al. 1987). Exogenous ACTH moderately decreases FSH levels in intact male rats, so the truth-table value for FSH with exogenous ACTH was set to 0.40 (Mann, Free et al. 1987). Exogenous ACTH administration in castrated male rats produces no change in LH levels, so the truth-table value for LH with ACTH was set to 0.50 for castrated males (Mann, Free et al. 1987). Exogenous ACTH results in a maximal decrease in testosterone levels in castrated male rats, so the truth-table value for testosterone with ACTH was set to 0.40 for castrated males (Mann, Free et al. 1987). Exogenous ACTH results in moderately elevates cortisol and progesterone levels in castrated male rats, so the truth-table values for cortisol and progesterone were set to 0.60 and 0.50, respectively, for castrated males (Mann, Free et al. 1987). Exogenous ACTH moderately decreases FSH levels in castrated males, so the truth-table value for FSH with exogenous ACTH was set to 0.40 for castrated males (Mann, Free et al. 1987).

Exogenous CRF projects to CRF1 and CRF2 receptors and elevates CRF levels in both males and females (Merchenthaler 1984). Exogenous CRF administration in both male and female humans has been found to moderately increase plasma ACTH and cortisol levels (Hermus, Pieters et al. 1984). The truth-table values for ACTH and cortisol with exogenous CRF were both set to 0.60.

Lesions to the PVN, amygdala, hippocampus and PFC all result in maximal decreases in PVN, amygdala, hippocampus, and PFC, respectively (Chang, Tran et al. 1980). The truth-table values for PVN, amygdala, hippocampus, and PFC, with PVN lesion, amygdala lesion, hippocampus lesion, and PFC lesion, respectively, were all set to 0.30. PVN lesion maximally reduces CRF levels and moderately reduces oxytocin levels in both male and female rodents, so the truth-table values for CRF and oxytocin with PVN lesion were set to 0.30 and 0.40, respectively (Bruhn, Plotsky et al. 1984, Antoni, Fink et al. 1990). Basal ACTH levels have also been found to moderately decrease with a PVN lesion in both male and female rodents, so the truth-table value for ACTH was set to 0.40 (Makara, Stark et al. 1981). PVN lesion has been found to maximally decrease melatonin levels in male rodents, so the truth-table value for melatonin with PVN lesion was set to 0.30 (Klein, Smoot et al. 1983). Adrenal gland activity has been found to moderately decrease with PVN lesion in both male and female rodents, so the truth-table value for adrenal gland was set to 0.40 (Makara, Stark et al. 1981).

The combination of PVN lesion and stress results in a moderate increase in CRF, ACTH,

and cortisol in both males and females (Makara, Stark et al. 1981, Bruhn, Plotsky et al. 1984, Makara 1992). The truth-table values for these were set to 0.60. Amygdala lesion and stress has been shown to lead to a moderate increase in CRF, ACTH, and cortisol in male subjects, so the truth table values for these were also set to 0.60 (Sakanaka, Shibasaki et al. 1986, Van de Kar, Piechowski et al. 1991, Feldman, Conforti et al. 1994). However, lesions of the PFC and hippocampus combined with stress lead to maximal elevations of ACTH and cortisol in male subjects (Jacobs, Wise et al. 1974, Herman, Schafer et al. 1989, Jacobson and Sapolsky 1991, Diorio, Viau et al. 1993, Herman, Cullinan et al. 1995). We set the truth-table values for ACTH and cortisol with PFC lesion/Stress and Hippocampus lesion/stress to 0.70.

The combination of PVN lesion and a 5HT1A receptor agonist prevented the rise in ACTH observed with the agonist by itself in male rats, so the truth-table value for ACTH with PVN lesion/Gepirone was set to 0.50 (Bluet Pajot, Mounier et al. 1995).

The Dexamethasone/CRF test is widely used in depression research to detect HPA axis dysfunction (Rush, Giles et al. 1996, Kunugi, Ida et al. 2006, Heim, Mletzko et al. 2008). CRF is injected after pretreatment with Dexamethasone (Kunugi, Ida et al. 2006). In normal control subjects, ACTH and cortisol secretion does not increase, but in stressed subjects, this test shows moderate increases in ACTH and cortisol secretion (Hohnloser, Von Werder et al. 1989, Kunugi, Ida et al. 2006, Heim, Mletzko et al. 2008). This was found for both males and females. We therefore set the truth-table values for ACTH and cortisol with Dexamethasone/CRF to 0.50, and the truth-table values for ACTH and cortisol with Dexamethasone/CRF/stress to 0.60.

Acute restraint stress with acute SSRI has been found to moderately increase AVP levels in male rodents, so the truth-table value for AVP with SSRI/stress was set to 0.60 (Hesketh, Jessop et al. 2005). Oxytocin and CRF levels moderately increase with SSRI/stress in male rodents, so the truth-table values for oxytocin and CRF with SSRI/Stress were set to 0.60 (Hesketh, Jessop et al. 2005). The combination of SSRI/Stress maximally increases ACTH and cortisol in male rodents, so the truth-table values for ACTH and cortisol were set to 0.70 with SSRI/Stress (Hesketh, Jessop et al. 2005). SSRI/Stress has been found to maximally increase NE levels in male rodents, so the truth-table value for NE with SSRI/stress was set to 0.70 (Page and Abercrombie 1997).

The combination of an SSRI and a 5HT1AR antagonist (SSRI/WAY) maximally increases 5HT levels in male rodents, so the truth-table value for SSRI/WAY was set to 0.70 (Arborelius,

Nomikos et al. 1996). The combination of an SSRI and WAY produces no change in DR firing rate from baseline in male and female rodents, so the truth-table value for DR with SSRI/WAY was set to 0.50 (Arborelius, Nomikos et al. 1995, Hajos, Gartside et al. 1995) (Evrard, Laporte et al. 1999)

Co-administration of an SSRI and Bupropion (SSRI/Bupropion) has been found by the Blier group to double DR firing rate and decrease LC firing rate by 60% in male rodents (Ghanbari, El Mansari et al. 2010). The truth-table values for DR and LC with SSRI/Bupropion were set to 0.60 and 0.40, respectively. SSRI/Bupropion have been found to moderately increase 5HT, NE and DA levels in male rodents, so the truth-table values for 5HT, NE and DA with acute SSRI/Bupropion were set to 0.60 (Li, Perry et al. 2002).

The Blier group found that the combination of an SSRI and Aripiprazole (SSRI/Aripiprazole) produces no significant change in the firing rates of DR or VTA neurons, but decreases LC neuron firing by 26% in male rodents (Chernoloz, El Mansari et al. 2009). The truth table values for DR, LC, and VTA with SSRI/Aripiprazole were set to 0.50, 0.40, and 0.50, respectively.

The Blier group found that the combination of an SSRI and Quetiapine (SSRI/Quetiapine) produces a 65% decrease in DR neuron firing and a 27% increase in LC neuron firing in male rodents (Chernoloz, El Mansari et al. 2012). The truth table values for DR and LC with SSRI/Quetiapine were therefore set to 0.40 and 0.60, respectively.

The combination of Reboxetine and fearful stimuli (fearful faces) has been found to moderately increase amygdala activity in males and females in fMRI experiments (Onur, Walter et al. 2009). The truth-table value for amygdala with Reboxetine/Stress was set to 0.60. The combination of Reboxetine and stress in male rodents has been found to produce no change in 5HT levels, maximally increases NE levels, and moderately increase DA levels (Page and Lucki 2002). The truth-table values for 5HT, NE and DA with Reboxetine/Stress were set to 0.50, 0.70, and 0.60, respectively.

Estrogen is a hormone input that projects to alpha and beta estrogen receptors in the model (Shughrue, Lane et al. 1997). Estrogen administration in both male and female intact rats has been shown to moderately increase DR neuron activity, so the truth-table value for DR was set to 0.60 for exogenous estrogen (Robichaud and Debonnel 2005). Estrogen produces no change CRF or

AVP levels in castrated male rats, so the truth-table values for CRF and AVP with estrogen were set to 0.50 for castrated males (Patchev, Hayashi et al. 1995).

Testosterone projects to the testosterone receptor in the model. Acute (3-day) administration of testosterone moderately increases DR neuron firing in both male and freely cycling female rats, so the truth-table value for DR with testosterone was set to 0.60 (Robichaud and Debonnel 2005). Testosterone administration to male rats was found to moderately increase 5HT and DA levels, so the truth-table values for 5HT and DA were set to 0.60 (de Souza Silva, Mattern et al. 2009).

Administration of hCG to intact male rats has been shown to moderately increase testosterone levels, so the truth-table value for testosterone was set to 0.70 (Saez, Morera et al. 1977). The combination of hCG and Dexamethasone as well as the combination of hCG and Corticosteroid to male testicular cell culture were both found to moderately decrease testosterone levels, so the truth-table values for testosterone with hCG/Dex and hCG/Corticosteroid were set to 0.50 (Bambino and Hsueh 1981).

ER-beta agonist projects to the Beta estrogen receptor. Administration of the ER-beta agonist to intact male rodents produces no change in testosterone levels, so the truth-table value for testosterone with ER-beta agonist was set to 0.60 (Patisaul, Burke et al. 2009). ER-beta agonist moderately increases 5HT and DA levels after 3-hours of administration in male rodents, so the truth-table values for 5HT and DA were set to 0.60 with acute ER-beta agonist (Hughes, Liu et al. 2008).

ER-alpha agonist projects to the Alpha estrogen receptor. Administration of the ER-alpha agonist to intact male rodents produces no change in testosterone levels, so the truth-table value for testosterone with ER-alpha agonist was set to 0.60 (Patisaul, Burke et al. 2009).

Exogenous AVP binds to V1A receptors in the model. Exogenous AVP has been found to moderately increase ACTH and cortisol levels in male humans, so the truth-table values for ACTH and cortisol with Exogenous AVP were set to 0.60 (Hensen, Hader et al. 1988).

Exogenous GnRH is a hormone input that binds to the GnRH receptor. Exogenous GnRH administration for three days to intact male rats moderately increases LH, FSH, and testosterone levels, so the truth-table values for LH, FSH and testosterone with exogenous GnRH were set to 0.60, 0.60, and 0.70 (Bruni, Huang et al. 1977, Mann, Free et al. 1987).

The combination of Exogenous ACTH and GnRH resulted in no change in serum testosterone levels in intact male rats, so the truth-table value for testosterone with Exogenous ACTH/GnRH were set to 0.60 (Mann, Free et al. 1987). The combination of exogenous ACTH and GnRH resulted in a moderate increase in LH levels in intact male rats, so the truth-table value for LH with exogenous ACTH/GnRH was set to 0.60 (Mann, Free et al. 1987).

The combination of ADX, exogenous ACTH and exogenous GnRH produces a moderate increase in LH levels in intact male rats, so the truth table value for LH with ADX/ACTH/GnRH was set to 0.60 (Mann, Free et al. 1987).

The combination of ADX and exogenous ACTH produces no change in testosterone levels of intact male rats, so the truth-table value of testosterone with ADX/ACTH was set to 0.60 (Saez, Morera et al. 1977, Mann, Free et al. 1987).

The combination of ADX/GnRH produces no change in testosterone levels in intact male rats, so the truth-table value for testosterone with ADX/GnRH was set to 0.60 (Mann, Free et al. 1987).

Corticosterone is a hormone input that projects to MC and GC receptors in the model. Corticosterone treatment moderately decreases adrenal gland weight in male rats, so the truth-table value for adrenal gland was set to 0.40 with corticosterone (Mann, Free et al. 1987). Serum LH levels were found to be unaffected by corticosterone in male rats, so the truth-table value for LH was set to 0.50 with corticosterone (Mann, Free et al. 1987). Testosterone levels were found to moderately decrease with acute corticosterone in male rats, so the truth-table value for testosterone with corticosterone was set to 0.50 (Mann, Free et al. 1987).

Cortisol infusion in castrated male Rhesus monkeys resulted in a maximal rise in cortisol levels, so the truth-table value for cortisol was set to 0.70 for cortisol infusion in castrated males. Cortisol infusion in castrated male Rhesus monkeys moderately decreases FSH and LH levels, but the addition of GnRH to the Cortisol infusion in castrated males results in in normal FSH and LH levels. The truth-table values for FSH and LH for cortisol infusion in castrated males were set to 0.40 and the truth-table values for FSH and LH for cortisol infusion in castrated males and GnRH were set to 0.50 (Dubey and Plant 1985).

The combination of corticosterone/GnRH moderately increases LH levels, does not change testosterone levels or testes size, and decreases adrenal gland size in male rats (Mann, Free et al.

1987). The truth-table values for LH, testosterone, testes, and adrenal gland were set to 0.60, 0.50, 0.50, and 0.40, respectively, with corticosterone/GnRH.

Castration has an inhibitory projection to the testes in the model. Castration has been found to maximally decrease testosterone levels and produce no change in DR neuron firing rate, so the truth-table value for testosterone was set to 0.40 and for DR was set to 0.50 (Robichaud and Debonnel 2005). Castration in intact male rats has also been found to moderately increase LH, FSH and progesterone levels, so the truth-table values for LH, FSH and progesterone with castration were set to 0.60, 0.60, and 0.50, respectively (Schwartz and Justo 1977, Mann, Free et al. 1987).

Exogenous 5HT injections in intact male rats increases 5HT levels and decreases testis weight, Gepso the truth-table value for 5HT was set to 0.60 and for testis was set to 0.40 with acute 5HT exogenous. Exogenous 5HT also increases LH and FSH levels, but decreases testosterone levels. The truth-table values for LH and FSH were set to 0.60, and for testosterone was set to 0.50 for exogenous 5HT (Hedger, Khatab et al. 1995).

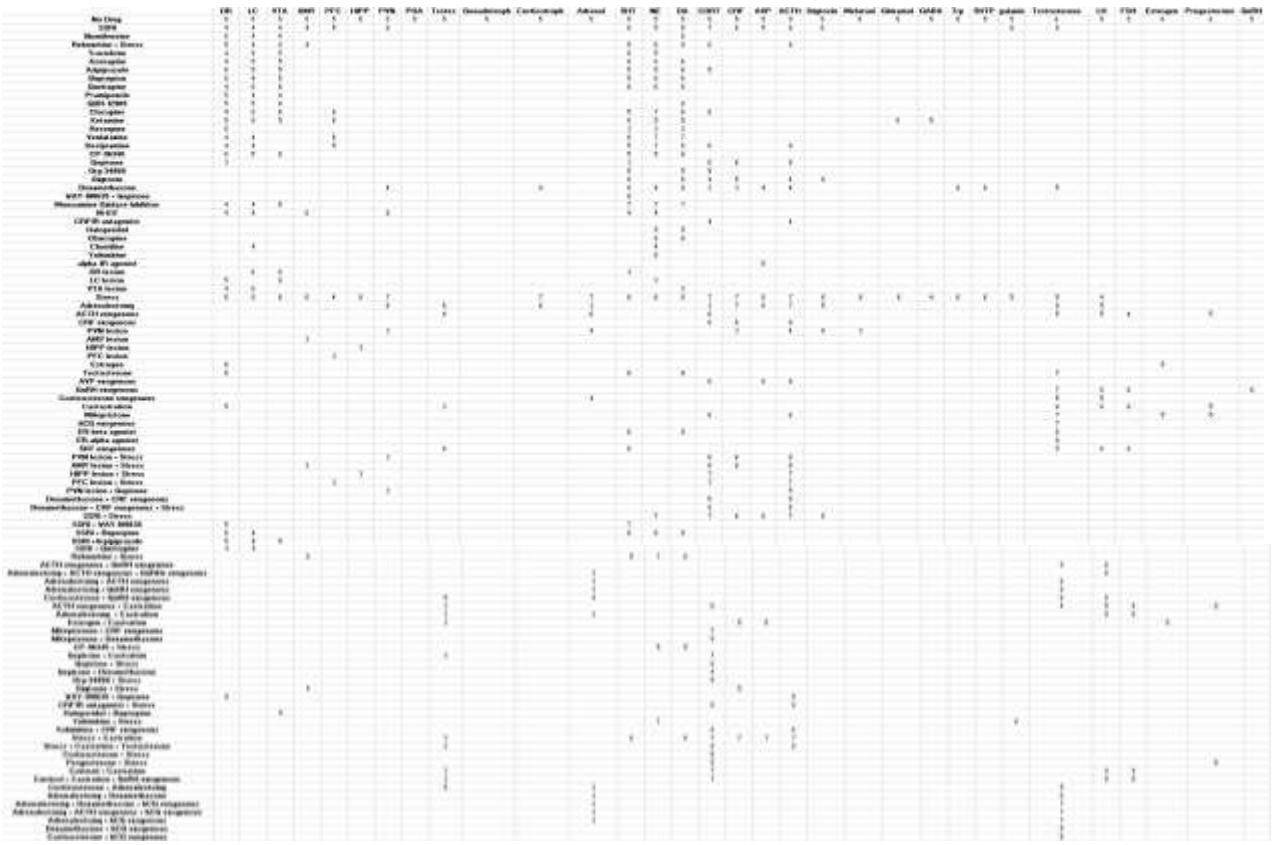
B.9 COMPLETE MS-MODEL TRUTH-TABLE

The MS-model truth table spreadsheet is below. All truth-table values were divided by 10 in the program code.

	DR	LC	YTA	AM	PF	hipp	PVN	Pleas	Adren	SHT	NE	DA	cortis	CRF	AVP	ACTH	Dat	MT	glu	GABA	Trp	SHTP	gal
No Drug	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
SSRI	4	4	4	4	5		6			6	5	5	7	6	5	7	6						8
Nomifensine	5	4	4									6											
Reboxetine	5	4	4	4						5	6	6	6			6							
Trazodone	4	6	5							6	5												
Asenapine	4	5	5							6	6	6											
Aripiprazole	5	5	5							5	5	6	5										
Bupropion	5	4	4							5	6	6											
Quetiapine	4	6	6							6	6	6											
PPX	5	4	4																				
GBR	5	5	4									6											
Clozapine	4	6	6		6					5	7	6	6										
Ketamine	5	6	5		6					6	5	5							6	5			
Reserpine	6	6								3	3	3	5										
Venlafaxine	4	4			6					6	7	7											
Desipramine	4	4			5					5	7	6	6										
CP	6	5	6							5	5	6											
Gepirone	3									3			6	6		6							
RU																5							
Org										5		5	5										
Oxytocin										6	5	6	4	5		4							
Dexamethasone								4	4	6	4	6	3	3	4	4	5				6	6	
VAY										6													
MAOI	4	4	5							7	7	7											
MS17	4	4		6			6			4	4												
CRFIR ant													4			4							
Haloperidol											5	5											
Olanzapine											6	6											
Clonidine		4									4												
Yohimbine											6												
DR lesion		6	6							3													
LC lesion	5		6								3												
YT lesion	4	6										3											
Stress	6	6	6	6	4	6	7	7	7	6	6	6	7	7	6	7	6	6	6	4	6	6	6
ADX							6	6	3				3	7	6	7	5						
ACTHex									6				6										
CRFex													6			6							
PVN lesion							3		4					3		4	4	3					
Amg lesion				3																			
Hipp lesion						3																	
PFC lesion					3																		
PVN lesion/Stress							3						6	6		6							
Amg lesion/Stress				3									6	6		6							
Hipp lesion/Stress						3							7			7							
PFC lesion/Stress					3								7			7							
Dex/CRF/Stress													6			6							
CRFIR antagonist/Stress													6			6							
Org/Stress													5										
Oxytocin/Stress				4							6	6	5		5								
ADX/Stress																7							
Reboxetine/Stress				6						5	7	6											
CP/Stress											5	5											
Yohimbine/Stress											7												8
Gepirone/Stress													6										
SSRI/Stress											7		7	6	6	7	6						
Dex/CRF													5			5							
ADX/Dex															4	4							
PVN lesion/Gepirone																5							
VAY/Gepirone	5															5							
Gepirone/Dex													4										
Bupropion/Haloperidol			5																				
Reserpine/Bupropion		6																					
SSRI/VAY	5									7													
SSRI/Bupropion	6	4								6	6	6											
SSRI/Aripiprazole	5	4	5																				
SSRI/Quetiapine	4	6																					

B.10 COMPLETE MSS-MODEL TRUTH-TABLE

The MSS-model truth table spreadsheet is below. All truth-table values were divided by 10 in the program code.



B.11 DETAILS ON TRAINING THE MS- AND MSS-MODELS USING GD

The MS-model takes the form of a recurrent network of units that all have the same sigmoidal (S-shaped, nonlinear but differentiable) activation function. This powerful computational formalism is a Turing-equivalent universal approximator that can be efficiently trained, via machine learning, to perform a broad range of desired, dynamic input-output transformations (Siegelmann and Sontag 1991). When used to model neural systems, the units in a recurrent network usually represent single neurons, or the average activity of the neurons in the same brain region (Anastasio 2010). In modeling and analysis of the transmitter and hormonal systems that mediate mood, however, multiple levels of organization must be taken into account that include not only brain regions and neurons but also proteins and small molecules.

In the MS-model, individual units represent the brain regions, transmitters, receptors, transporters, enzymes, precursors, metabolites, and hormones that are involved in the pathologies of anxiety and depression. Some individual units represented whole brain regions that are central to these pathologies. The monoaminergic neurotransmitter-producing regions (DR, LC and VTA)

were represented as single units because the majority of antidepressant drugs target these regions directly (Koenig and Thase 2009). The HPA axis regions (PVN, pituitary gland, and adrenal gland) were represented as single units in order to incorporate the effects of the stress response in our analysis. The amygdala, prefrontal cortex (PFC), and hippocampus were represented because these regions are implicated in regulation of the HPA axis, and because they are also implicated in the antidepressant response itself through their involvement in cognitive control (Dinan 1996, Malagie, Trillat et al. 1996, Godlewska, Norbury et al. 2012, Albert, Vahid-Ansari et al. 2014).

Single units also represented key neurotransmitters (e.g. 5HT, NE, and DA) and hormones (e.g. cortisol (CORT) and oxytocin (Oxt)), and many of the key transmitter receptors, transporters, and enzymes that are transmitter-system components (TSCs).

Representing neurobiological entities (brain regions, transmitters, receptors, etc.) as single units enabled the model to represent the level (of activity, expression, concentration, etc.) of that entity in the whole brain, or in specific brain regions as appropriate. The 5HT unit, for example, represented the brain serotonin level, which is the major neurobiological endpoint for antidepressant action. The weights of the connections between the units also had specific identities in the model. For example, the effectiveness of the 5HT autoreceptor in inhibiting DR neurons was represented in the model by the absolute value of the inhibitory weight of the 5HT1A receptor (5HT1AR) unit onto the DR unit.

Relative to the overall number of network weights, a very small number of weights were of great significance because they represented TSCs whose efficacies, or strengths (expression levels, sensitivities, concentrations, synaptic locations, etc.), are known to adapt under chronic stress or chronic antidepressant administration. All of the weights in a trained network represent the normative strengths of influences of specific neurobiological entities on each other. The weights of the adaptable TSCs specifically were further adjusted to analyze the possible modes of adaptation to chronic stress, drugs, or hormones in the model.

In describing neural networks it is necessary to distinguish inputs/outputs to/from the network overall, and inputs/outputs to/from individual units in the network. Units are categorized as input, output, or "hidden units." There were 40 input units that provided input to the overall network. They take on assigned values and project to other units but do not receive connections from other units. Hidden and output units receive connections from input units and from each other. There were 23 output units that provided the output of the overall network. Output units are

distinguished from hidden units in having targets (desired outputs). Hidden units have neither assigned nor desired values. The network consisted of 102 total units (input, hidden, and output).

Individually, the activity of each unit is a function of its inputs from the other units (this is not true for input units that do not receive inputs from other units). Each sending unit provides inputs to receiving units that are equal to the product of the sending unit's activity level and the value of the weight (positive or negative) of the connection from the sending unit to the receiving unit. The net input to a receiving unit is the sum of the weighted inputs from all its sending units. The activity level of a unit is the value of its net input (i.e. weighted input sum) after it has passed through the sigmoidal activation function, which "squashes" the net input sigmoidally in the range between 0 and 1. The value of the sigmoidal squashing function for net input 0 is 0.50 (the midpoint of the 0−1 range).

The connection weights from the input, hidden, and output units to the hidden and output units are organized into the network weight matrix. The weight matrix consisted of 61 rows and 102 columns for a total of 6222 weights. Any input, hidden, or output unit could project to any hidden or output unit, but various distinctions between specific classes of connection weights were made in order to satisfy modeling goals.

The subject of the MS-model is the behavior of the monoaminergic transmitter systems and the stress hormone system (i.e. the monoamine-stress system) as they relate to the pathophysiology of depression. This behavior involves heavy interaction between the 3 monoaminergic transmitter systems and the stress hormone system, but also involves interactions between those systems and many other systems throughout the nervous system. The MS-model is therefore focused on the interactions between the monoaminergic transmitter and stress hormone systems, but also represents many other interactions that are included to ensure that model behavior is in line with a large set of empirical observations on the monoamine-stress system, as described in the literature.

In order to foreground monoamine-stress system interactions in the model, 3 classes of connection weights are distinguished: canonical, structure, and non-structure. Canonical weights are the weights of the known connections between units representing key components of the monoamine-stress system, such as the weight from the DR to 5HT, representing the effectiveness of the DR in producing 5HT. There were 23 canonical weights. Structure weights are the weights of the connections between units representing neurobiological entities that are also known to

interact empirically but are not canonical weights, such as the weight from DR to galanin, representing the effectiveness of the DR in co-releasing galanin. There were 305 total structure weights. Non-structure weights denote all other connection weights; they may or may not represent as yet unidentified interactions that actually do occur neurobiology. There were 5894 non-structure weights in total. The three classes of weights are treated differently during model training.

Two data structures were needed in order to construct and train the MS-model: a structure matrix and a truth table. Both the structure matrix and the truth table were compiled via a comprehensive literature search. The structure matrix is a two-dimensional matrix, coextensive with the network weight matrix, which specifies which neurobiological entities in the model are known to interact with which others, and their valance (positive or negative) if also known. The structure matrix designates all structure and canonical weights in the model using non-zero integers. Non-structure weights take value 0 in the structure matrix.

The truth table is an array of input/desired-output training patterns that specifies how specific experimental manipulations, which are represented as patterns of network inputs, are known to affect specific neurobiological endpoints, which are represented as patterns of desired network outputs. Each row of the truth table represents the statistically significant results of one or more actual experiments. Inputs are either present or absent (1 or 0) and outputs are assigned discrete levels between 0.30 and 0.70. Outputs could either decrease maximally, decrease moderately, have no change, increase moderately, or increase maximally, corresponding to desired-output values of 0.30, 0.40, 0.50, 0.60, and 0.70, respectively. The complete truth table has 66 input/desired output patterns.

The MSS-model has a "foreground" and a "background." The foreground is a representation of the main components of the 3 monoaminergic-transmitters systems and of the stress- and sex-hormone systems. The background is a representation of most of the related neural, transmitter, and hormonal systems that are known to interact with the monoaminergic-transmitter, stress, and sex hormone systems but on which fewer data are available. Single elements of the MSS-model represented key brain regions including all of the foreground brain regions (e.g. DR, LC, PVN, and POA) and key molecular components of the interacting biological systems including receptors, transporters, enzymes, precursors, metabolites, and the transmitters and hormones themselves.

The MSS-model was constructed, parameterized, run, adapted, and analyzed in the same way as the MS-model. Methodological details can be found in (Camacho, Vijitbenjaronk et al. 2018). Computational and analytical procedures will be briefly summarized here and any differences with the MS-model will be noted.

The MSS-model takes the form of a recurrent network of nonlinear elements or "units." All of the units have the same sigmoidal (S-shaped) nonlinearity that bounds their activity between 0 and 1 and produces an output of 0.50 for 0 input. Units in the network are classified as input, output, or "hidden." Input units send connections to hidden and output units, while hidden and output units send connections to each other but not to input units. Input values are preassigned to input units, and desired (or target) values are preassigned to output units during training. Hidden units have no preassigned values. All connections in the network are weighted. On each network update, each hidden or output unit computes the sum of its weighted inputs from other units and applies the sigmoid to its weighted input sum. Typically, networks are updated for 100 time steps.

The units in the model corresponded to regional or brain-wide biological variables. Some single units represented the average activity of all of the neurons in specific brain regions including the foreground regions: DR, LC, VTA, PVN, and POA. Other single units represented brain levels of key transmitters (e.g. 5HT, NE, or DA) and hormones (e.g. cortisol (CORT) or testosterone (TEST)). Still others represented the overall brain "activity" (expression, sensitivity, concentration, etc., or combinations thereof) of key receptors, transporters, enzymes, and small molecules that constitute transmitter-system components (TSCs). While the units represented regional or brain-wide variables, the weights of the connections between units represented cellular-level variables. The effectiveness of the 5HT transporter (5HTT) in inhibiting 5HT levels, for example, was represented in the model by the absolute value of the inhibitory weight of the 5HTT unit onto the 5HT unit.

A small subset (precisely 13) of the connection weights represent cell-specific entities that known to adapt or adjust their strengths (through changes in expression, sensitivity, concentration, etc.) under chronic stress, or with chronic administration of drugs or hormones. These will be referred to as "adjustable TSCs." The adjustable-TSC weights were used to analyze adaptation (specifically, neuroadaptation) to chronic administration of drugs, hormones, and combinations in the MSS-model.

There were 132 total network units (54 input, 32 output, and 46 hidden units). The 77x130 network weight matrix organizes the connection weights from the input, hidden, and output units to the hidden and output units for a total of 10,010 connection weights. There are 3 major classes of connection weights in the MSS-model: canonical, structure, and non-structure.

The 36 canonical weights represent empirically known interactions between key elements of the foreground systems: monoaminergic system, HPA axis, and HPG axis. One canonical weight, for example, is the weight of the connection from the testes unit to the TEST unit. This canonical weight represents the efficacy of the testes in releasing testosterone. The 426 structure weights represent other empirically known interactions between elements of the background systems, such as the connection weight between the LC and galanin units, representing the efficacy of galanin co-released by the LC. The 9548 non-structure weights are all the other connection weights which represent interactions that have not been identified as yet and may or may not represent interactions that occur neurobiologically.

The MSS-model was constructed and parameterized on the basis of two data structures: a structure matrix and a truth table, both of which were populated through extensive literature review. The structure matrix is a 77x130 matrix that is coextensive with the network weight matrix, which specifies the canonical and structure connections between model units as well as their valence (positive or negative) if known.

The truth table is an array of input/desired-output training patterns that specifies how specific inputs (experimental manipulations such as drugs, stress, hormones, lesions, etc.) are known to affect specific output units (such as 5HT, CORT, or TEST level). Each row of the truth-table represents the results of at least one experiment. Inputs can be either present (1) or absent (0). Desired outputs specify maximal decrease, moderate decrease, no change, moderate increase, or maximal increase, corresponding to values of 0.30, 0.40, 0.50, 0.60, and 0.70, respectively.

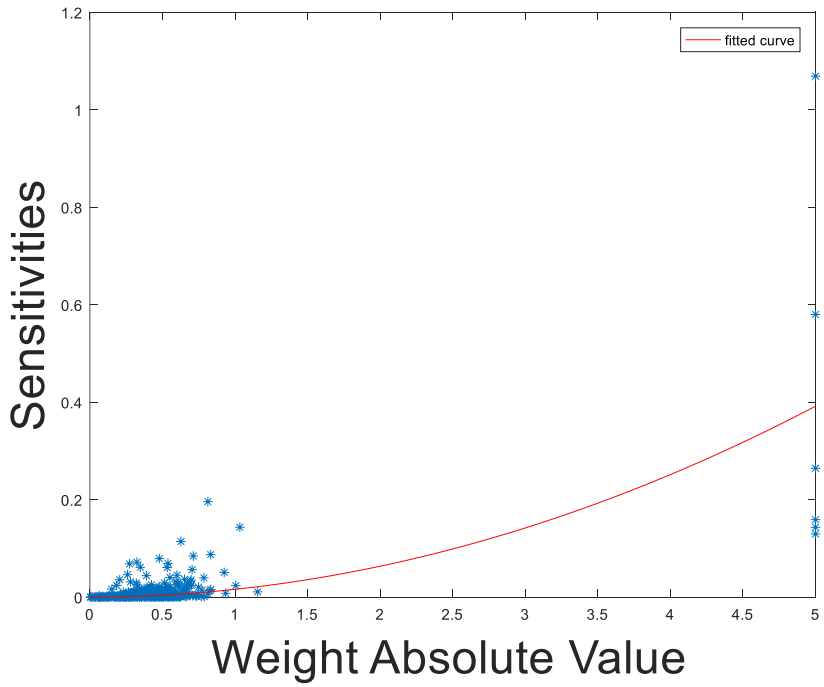
B.12 PRUNING METHODS

We were interested in pruning the networks in order to eliminate unneeded non-structure connections, and to minimize overfitting in order to increase the generalizability of model results. Two previously studied methods are pruning on the basis of the magnitude of the weight, or on the basis of sensitivity of the error to each individual weight. In the former, weights below a certain absolute value cutoff are removed. This is based on the idea that weights trained to a low value

should make a smaller contribution to model behavior (Rumelhart 1988). In the latter method, contribution to network behavior is measured explicitly as the sensitivity of the error to each individual weight. Weights below a certain sensitivity cutoff are removed (Mozer 1989). These methods are believed to produce comparable results and are commonly used to prune neural networks (Segee 1991).

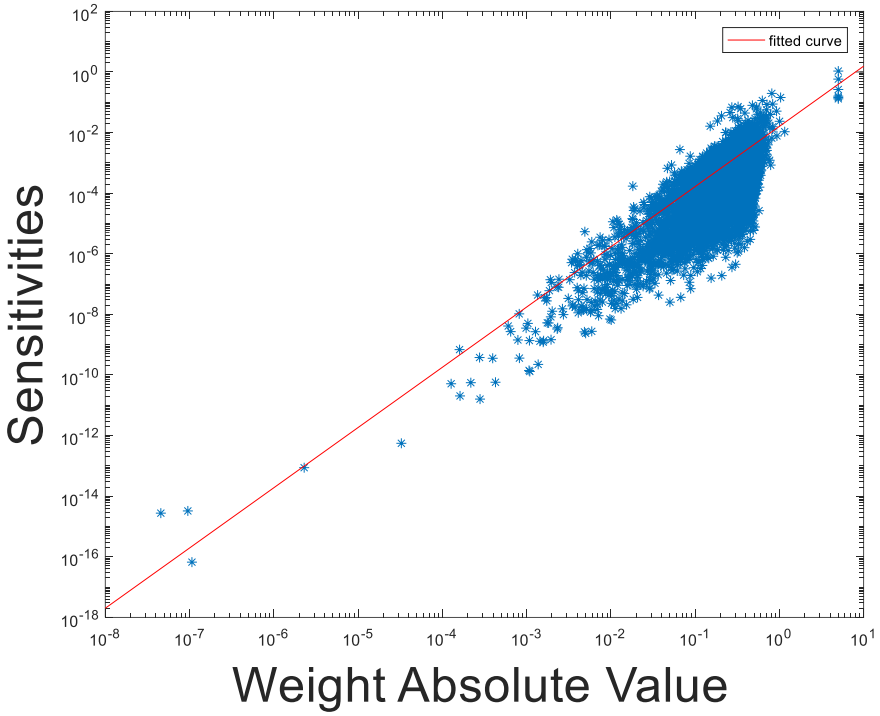
To evaluate the difference specifically for the MS-model between pruning on the basis of absolute value or sensitivity, we trained all connections in a network and plotted the sensitivity of each weight (y-axis) against the absolute value of each weight (x-axis). Figure A shows the relationship on a linear-linear plot while Figure B shows it on a log-log plot for a representative case. We found a very interesting power function relationship in all of 10 cases where the exponents ranged from 1.77 to 2.72 and the scale factors ranged from 0.012 to 0.026. The correlation coefficients ranged between 0.32 and 0.71.

A



The lack of perfect correlation between weight absolute values and sensitivity proves that pruning on the basis of absolute value and pruning on the basis of sensitivity would prune different weights from the networks.

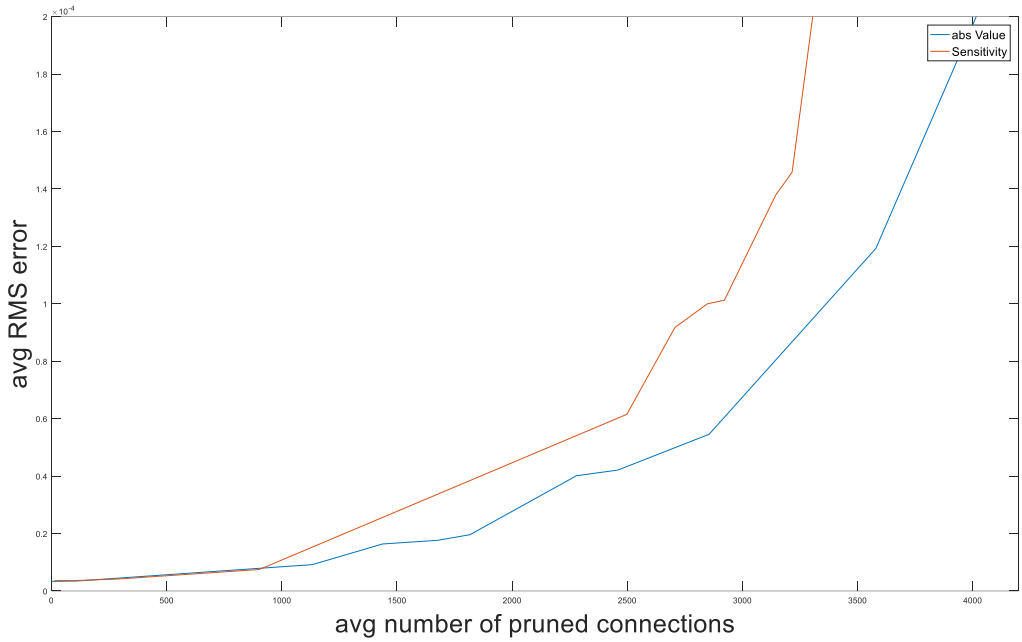
B



To determine which pruning strategy is better, non-structure connections of each of the ten original networks were pruned at various cutoffs according to the specified pruning criterion (absolute value or sensitivity), and the pruned network was then re-trained. During re-training, the structure connections were trained at the same fast learning rate (3) while the non-structure connections were trained at a learning rate that was an order of magnitude lower than that of the fast connections (0.30). The purpose of this was to favor strengthening connections that were known from the experimental literature. Non-structure connections were still trained because they were necessary to produce reasonable agreement with the training set.

A visual comparison of the effect of pruning on the basis of sensitivity or pruning on the basis of absolute value on RMS error is shown in Figure C. This plot has number of pruned connections on the x-axis and the average RMS error of the ten networks after pruning on the y-axis. It suggests that pruning on the basis of absolute value will eliminate the most connections while still maintaining a low RMS error over the entire truth table. Even though having a low RMS error is important for fitting truth-table information, the overall goal is for the model to predict novel drug combinations to improve antidepressant therapeutic efficacy. We evaluated if pruning on the basis of absolute value was still the ideal pruning method for this purpose.

C

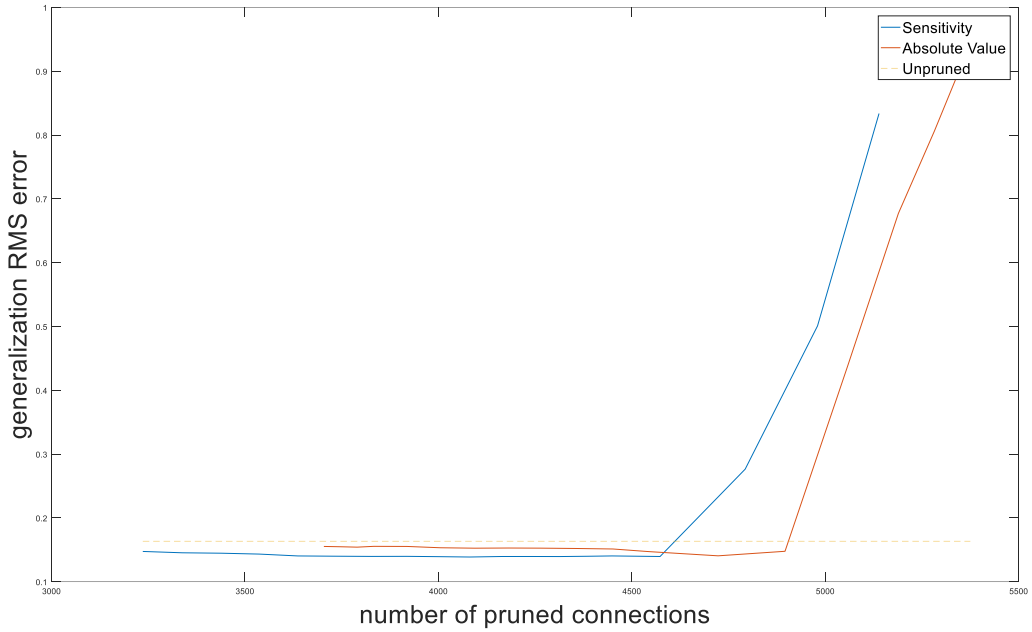


The best way to determine if a machine-learning procedure has indeed learned input-output relationships over its domain is to evaluate how well it generalizes to data that it was not trained on (Sietsma and Dow 1991). We then trained the model on only the single inputs by removing all of the combination inputs from the truth table (two inputs or more). We obtained ten fits trained only on single input data with an average RMS error of 9.53×10^{-18}. These ten fits were then pruned at 20 different cutoffs on the basis of absolute value and on the basis of sensitivity and re-trained as described in the previous subsection. The pruned and re-trained weight matrices were then given the drug combinations that were removed from the training set and their outputs were obtained and compared with experimental findings to produce an average RMS error. We found that the original, unpruned weight matrices had an average RMS error of 0.1637 over the untrained drug combination data.

Interestingly, we found that pruning could significantly decrease this average RMS error. We plotted the untrained drug-combination RMS errors versus the number of pruned connections to determine which pruning method can decrease this RMS value the most. Figure D shows that pruning on the basis of sensitivity will achieve better generalizability than pruning on the basis of absolute value. Specifically, we found the best method was pruning on the basis of sensitivity at a cutoff of $1 \times 10^{-3.35}$ pruned 4081 connections on average and produced an average RMS error over the untrained data of 0.139. The Mann-Whitney U test showed that this was significantly better

than the best result pruning on the basis of absolute value (p-value of 0.002). All further training sets were trained using the full truth table and pruned at a sensitivity cutoff of $1x10^{-3.35}$ and retrained using the retraining method described above. This optimized our MS-model to generalize on acute drug combinations that it was not trained on.

D



B.13 MS-MODEL ADJUSTABLE TSCS

Neuroadaptation was simulated by allowing the networks to adjust the strengths of the weights that are known to adjust under the conditions of the experiments from which the truth table was derived. The adjustable TSCs were a subset of the canonical weights. Configurations of adjusted TSCs that resulted in a reduction in network imbalance by bringing the most heavily trained brain regions (DR, LC, VTA, PVN) back toward their baseline values were considered adapted.

Number	Adjustable TSC	Polarity	References
1	5HT1AR to DR	–	(Blier and de Montigny 1987, Szabo and Blier 2001, El Mansari, Ghanbari et al. 2008, Ghanbari, El Mansari et al.

			2010, Rozeske, Evans et al. 2011)
2	AR2 to LC	−	(Szabo and Blier 2002, El Mansari, Ghanbari et al. 2008)
3	D2R to VTA	−	(Chernoloz, El Mansari et al. 2009, Katz, Guiard et al. 2010, Madhavan, Argilli et al. 2013)
4	5HTT to 5HT	−	(Lesch, Aulakh et al. 1993, Benmansour, Cecchi et al. 1999, Lau, Horschitz et al. 2008)
5	NET to NE	−	(Hebert, Habimana et al. 2001, Miner, Jedema et al. 2006, Pietrzak, Gallezot et al. 2013)
6	DAT to DA	−	(Neumeister, Willeit et al. 2001, Brunswick, Amsterdam et al. 2003, Kugaya, Seneca et al. 2003, Yang, Yeh et al. 2008)
7	GCR to PVN	−	(Pariante and Miller 2001, Barden 2004, Ladd, Huot et al. 2004)

8	GCR to Pituitary Gland	−	(Barden 2004, Ladd, Huot et al. 2004)
9	GCR to Adrenal Gland	−	(Barden 2004, Ladd, Huot et al. 2004)
10	CRF1R to Pituitary Gland	+	(Nikodemova, Diehl et al. 2002, Kageyama, Hanada et al. 2006)

B.14 MSS-MODEL ADJUSTABLE TSCS

A subset of the model transmitter-system components (TSCs) are known to be adaptable under the conditions of the experiments from which the truth table was derived. These 13 TSCs are referred to as "adjustable TSCs" and are comprised of canonical weights from each of the 3 systems (monoaminergic, stress-steroid, sex-steroid) in the model. Adjusted TSC configurations that reduced adaptation error by bringing responses of the most heavily trained brain regions (DR, LC, and VTA) back toward their baseline values were considered adapted.

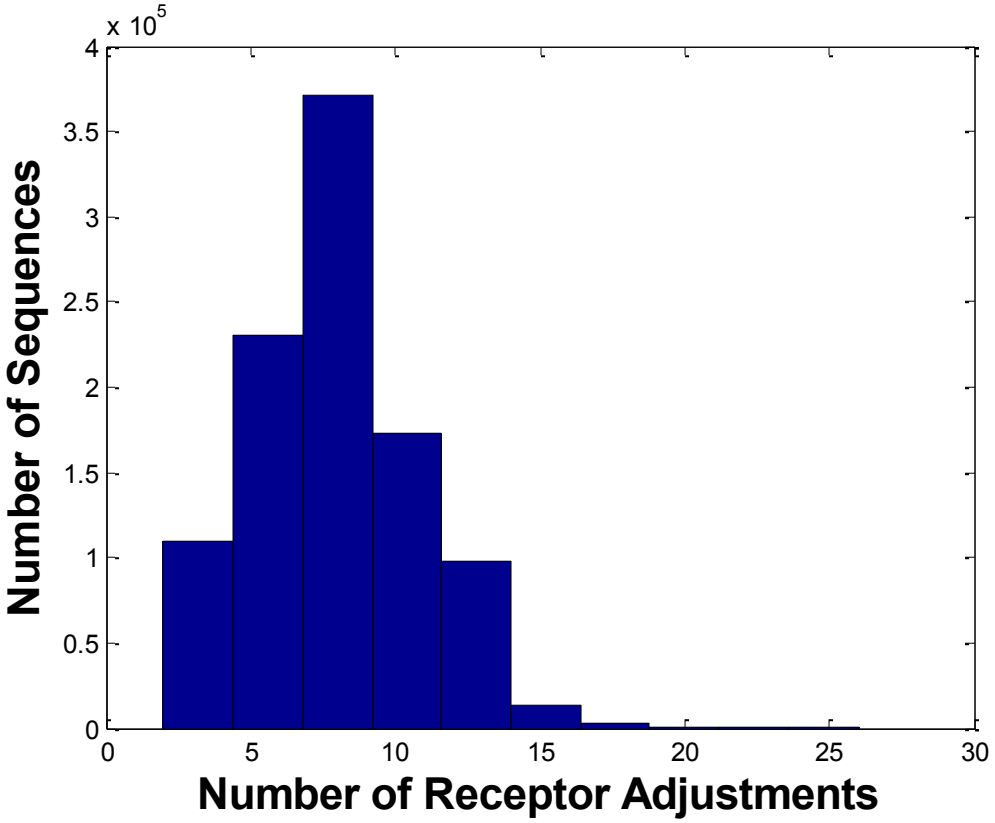
Number	Weight	Polarity	References
1	5HT1AR to DR	−	(Blier and de Montigny 1987, Szabo and Blier 2001, El Mansari, Ghanbari et al. 2008, Ghanbari, El Mansari et al. 2010, Rozeske, Evans et al. 2011)
2	AR2 to LC	−	(Szabo and Blier 2002, El Mansari, Ghanbari et al. 2008)
3	D2R to VTA	−	(Chernoloz, El Mansari et al. 2009, Katz, Guiard et al. 2010, Madhavan,

			Argilli et al. 2013)
4	5HTT to 5HT	−	(Lesch, Aulakh et al. 1993, Benmansour, Cecchi et al. 1999, Lau, Horschitz et al. 2008)
5	NET to NE	−	(Hebert, Habimana et al. 2001, Miner, Jedema et al. 2006, Pietrzak, Gallezot et al. 2013)
6	DAT to DA	−	(Neumeister, Willeit et al. 2001, Brunswick, Amsterdam et al. 2003, Kugaya, Seneca et al. 2003, Yang, Yeh et al. 2008)
7	GCR to PVN	−	(Pariante and Miller 2001, Barden 2004, Ladd, Huot et al. 2004)
8	GCR to Corticotroph	−	(Barden 2004, Ladd, Huot et al. 2004)
9	GCR to Adrenal Gland	−	(Barden 2004, Ladd, Huot et al. 2004)
10	AR to POA	−	(Handa, Kerr et al. 1996)
11	AR to Gonadotroph	−	(Bremner, Millar et al. 1994)
12	FSHR to Testes	+	(Catt, Baukal et al. 1979, Heckert and Griswold 1991)
13	LHR to Testes	+	(Belanger, Auclair et al. 1979, Catt,

			Baukal et al. 1979)

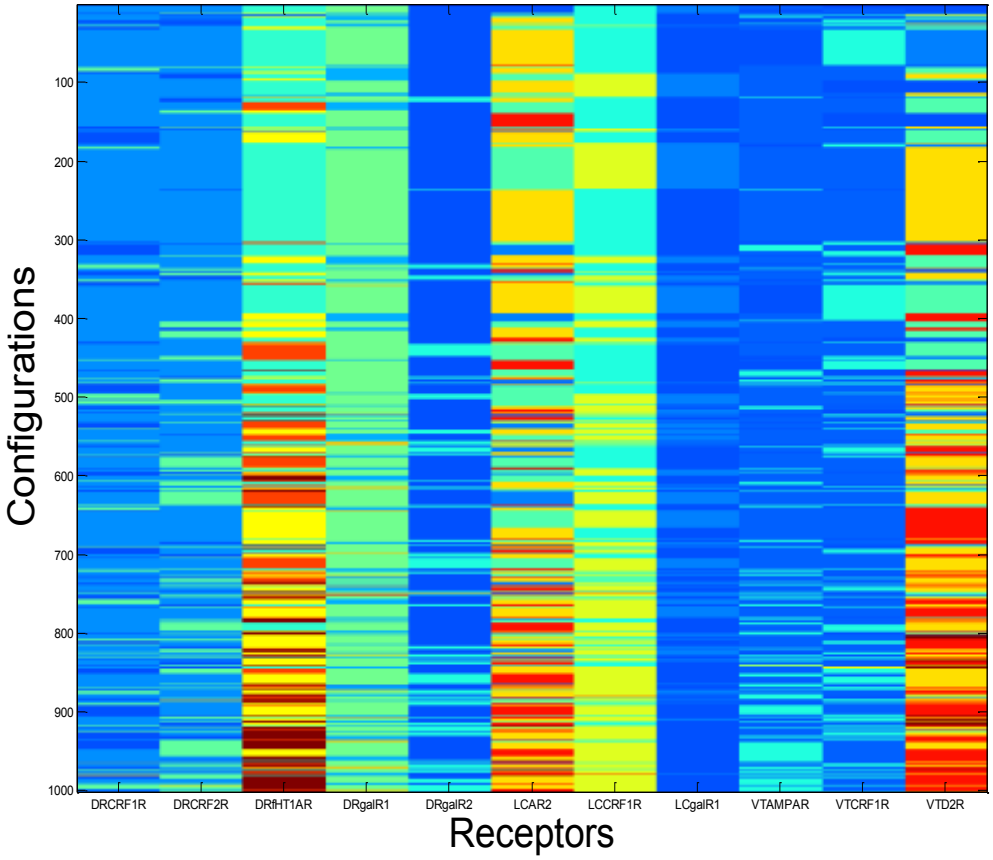
B.15 M-MODEL STRICTLY ERROR-REDUCING ADJUSTMENTS

The MATLAB version of the M-model was used for making TSC strength adjustments along single sequences in which adjustment of a randomly chosen TSC was retained only if it resulted in a homeostatic reduction in activation error. Here 1,000,000 randomly-ordered sequences of strictly error-reducing adjustments were allowed to continue until the M-model achieved terminal adaptation, in which further adjustments no longer reduced activation error with chronic Escitalopram. The histogram plots the number of sequences achieving terminal adaptation as a function of the number of adjustments. The mean number of adjustments is 7.90, the mode is 7, the median is 8, and the range is from 2 to 26.



The MATLAB version of the M-model was then used to make 1000 randomly-ordered, strictly error-reducing sequences of adjustments until further adjustments no longer reduced the activation error with chronic Escitalopram. This approach produced 1000 terminally adapted TSC-

strength configurations, which we plotted using a heat map. Each of 1000 rows is a vector of final receptor values for all 11 adjustable TSCs. The 1000 terminally adapted configurations were ordered by Euclidian distance from a reference vector of all 0s, which is shown in row 0. The 11 adjustable TSCs can adjust by 1 to any level between 0 and 10 for a total of 11^{11} or more than 285 billion possible TSC-strength configurations. This very small sample of 1000 terminally adapted configurations reveals considerable heterogeneity, and clearly shows that there are very many distinct configurations that are terminally adapted in the sense that further TSC strength adjustment will not further decrease activation error.



B.16 SETTING THERAPEUTIC CRITERIA

B.16.1 M-MODEL

Among the adapted TSC-strength configurations, we also searched for configurations that achieved certain levels of the monoaminergic transmitters. “Therapeutic” monoamine levels have not yet been determined unequivocally. For the M-model, we set our search criteria conservatively on the basis of the percentage changes in monoaminergic transmitter levels associated with

reduction in depression symptomology that we were able to find in the literature. We were unable to find reports of studies directly showing efficacy of SSRIs that also measure 5HT levels in the brain. However, both preclinical and clinical evidence has accumulated to support the hypothesis that the 5HT system is involved in the therapeutic action of SSRIs and several other antidepressant drugs by elevating 5HT (reviewed in (Blier and de Montigny 1994)). Specifically, one study found that chronic Escitalopram increases 5HT levels in the prefrontal cortex to 422% of baseline (Ceglia, Acconcia et al. 2004). Also, it has repeatedly been found that chronic SSRI use elevates 5HT levels to around 400% (Romero, Celada et al. 2003, Beyer and Cremers 2008). We considered adapted TSC strength configurations for which 5HT was elevated by more than 400% of normal baseline to be therapeutic.

Rodents undergoing the forced swim test (which produces "behavioral despair") that were given Reboxetine [a norepinephrine reuptake inhibitor, (NERI)] and demonstrated decreased immobility (i.e., antidepressant effect) were found using microdialysis to increase NE levels to 212% of baseline (Page, Brown et al. 2003, Can, Dao et al. 2012). Rats that demonstrated alleviation of depressive symptomatology (measured through increased locomotor activity) due to administration of St. John's Wort were found to increase DA levels to 140% of baseline in the prefrontal cortex (Yoshitake, Iizuka et al. 2004). We considered adapted TSC configurations for which NE or DA were elevated by more than 200% of normal baseline to be therapeutic. These therapeutic cutoffs were used in Maude analysis of the M-model to identify TSC strength configurations with therapeutic elevations in the monoamines.

B.16.2 MS- AND MSS-MODELS

Therapeutic criteria were set using the same criteria as described in the MS-model (Camacho, Vijitbenjaronk et al. 2018). Briefly, chronic SSRI administration has been shown to double 5HT levels associated with acute SSRI administration (Ceglia, Acconcia et al. 2004). The desired baseline 5HT level was set to 0.50, and the desired 5HT output for acute SSRI was set to 0.60. The therapeutic 5HT floor was therefore set to 0.70 in order to double the increase of 0.10 observed with acute SSRI. For consistency, 0.70 was also used as the therapeutic floor for NE and DA although therapeutic NE and DA levels resulting from chronic antidepressant administration have not been determined. Because the high CORT levels associated with acute SSRI have been found to decrease with chronic SSRI (Ruhe, Khoenkhoen et al. 2015), the therapeutic ceiling for

CORT was set to 0.70, which is the level assigned to the desired, high CORT level due to acute SSRI in the model.

B.17 DETAILS ON TEMPORAL-LOGIC MODEL-CHECKING PROCEDURE

Temporal logic is a system of symbols and rules for representing and reasoning about propositions examined in terms of *time*. Temporal logic can be used to express a unary occurrence through time, such as "I am *always* strong" or "I will *eventually* be strong," and it can also be used to express binary relationships between two different statements, such as "I will be strong *until* I stop going to the gym." Maude is an excellent tool for assessing the validity of temporal-logic propositions, by telling us whether or not a particular proposition is true (e.g., to address questions such as: Is it true that "I am *always* strong?").

Temporal relationships in models of neurobiological processes can be examined in Maude to determine if a particular statement is true, or if a particular relationship between two (or more) statements is true. In a system as complicated as the MS- and MSS-models, where there are hundreds of thousands of TSC-strength adjustment pathways being elaborated to depth 6, temporal-logic model-checking in Maude is an extremely useful tool for determining if properties of neurobiological interest have certain relationships with one another as neuroadaptive pathways are elaborated. We implemented temporal-logic model-checking procedures into Python in order to maximize computational efficiency. Extensive cross-checking ensured that Maude and Python temporal-logic analyses were in agreement.

In all three models, each state has a unique TSC-strength configuration associated with a unique pattern of neural-region activities and neurotransmitters and hormone levels. Temporal-logic analysis can be used to ascertain the validity of temporal relationships between these states in terms of their properties (e.g., neurotransmitter levels, hormone levels, receptor strengths). Python can be used to evaluate these relationships by elaborating the tree of TSC strength configurations and searching for a counterexample to the temporal-logic model-check specified. If the analysis does not find a counterexample, the result is a Boolean "true." If a counterexample is found, then the counterexample state is listed and followed by the statement "false."

All temporal-logic model-checks were carried out to a depth of 6 over all 3 networks for each model and only the results that were consistent across all 3 networks are reported in this document. The neurobiological relationships that were examined, as well as their symbolic representations, are all reported in the Results chapter of the main text.

B.18 HARDWARE CONSIDERATIONS

B.18.1 M-MODEL

The most computationally intensive procedures undertaken for this analysis were GA optimizations (in MATLAB) and state-space searches (in Maude). Both of these procedures are immanently parallelizable. MATLAB has built-in options for parallelizing GA optimizations. Unfortunately, options for parallelizing Maude searches were not available. Multiple computers were used for computational analysis. All computers had dual-core, Intel-based processors but varied in number of processors, memory capacity, and operating system.

All MATLAB GA optimizations were carried out on 16-processor Intel Zeon machines with 2, 2.60 GHz cores per processor (32 cores total) and 128GB of RAM under the Windows 7 operating system. The machines were made available by the Beckman Institute Visualization Lab. A single GA optimization that evolved a population of 100, 76-element parameter sets until the change in the fitness between generations was less than a tolerance of 10^{-12} took about 3 h on those 32-core VizLab machines.

Although parallelized Maude search was not an option, we did run multiple, serial Maude searches simultaneously on cores distributed over several machines. Maude searches were run on an Intel-inside CORE i7 processor with 2, 2.69 GHz cores and 8.00 GB of RAM under the Windows 8 operating system, and on an Intel Core 2 Duo CPU processor with 2, 2.33 GHz cores and 4.00 GB of RAM under the Windows 7 operating system. Maude elaboration and search of a state-transition tree having up to 11,155 states (i.e., TSC-strength configurations) took between 4 and 22 h on each core of those dual-core machines. Given the large number of optimizations and searches necessary both to establish the paradigm and then generate the actual results, these hardware constraints largely determined the complexity of the model that we could optimize (76 parameters per optimization) and the depth of the state-transition tree we could exhaustively search (to level 3 or up to 11,155 states per search).

B.18.2 MS-MODEL

All MATLAB computational procedures were performed on an Intel Core 2 Duo CPU processor with 2, 2.33 GHz cores and 4.00 GB of RAM under the Windows 7 operating system, an Intel-inside CORE i7 processor with 2, 2.69 GHz cores and 8.00 GB of RAM under the Windows 8 operating system, and an Intel Core i7 processor with 4, 4.00 GHz cores and 32.00 GB of RAM under the Windows 10 operating system. MATLAB was used for training, pruning,

enumerating, and analyzing all adjustable-TSC configurations with up to 6 adjustments in TSC strength, generation of all histograms and heatmaps, and FRIWA analysis. Training a network (100 time steps, $1x10^6$ iterations, 66 training patterns) took between 20 and 25 minutes. Exhaustively computing full sets of adjustable TSC configurations to degree 6 took 1 minute. Computational overhead (memory limitations) prevented computing the full set to degree 7. Checking the set of TSC-strength configurations for neuroadaptation to chronic drug or hormone combinations in each of the 3 representative networks took 8 minutes per network using MATLAB.

Python was used for enumeration of TSC-strength configurations and LTL analysis. Python search and LTL analysis of TSC-strength configurations having 382,747 states took 34 seconds on one quad-core Intel Core i5 processor. For subsequent model checks where steady-state values had been cached, model checks took an average of 3.10 seconds. Python enumeration of TSC-strength configurations was limited to degree 6 for consistency with the MATLAB analysis and because the results were unlikely to be different for degree 7 than for degree 6.

B.18.3 MSS-MODEL

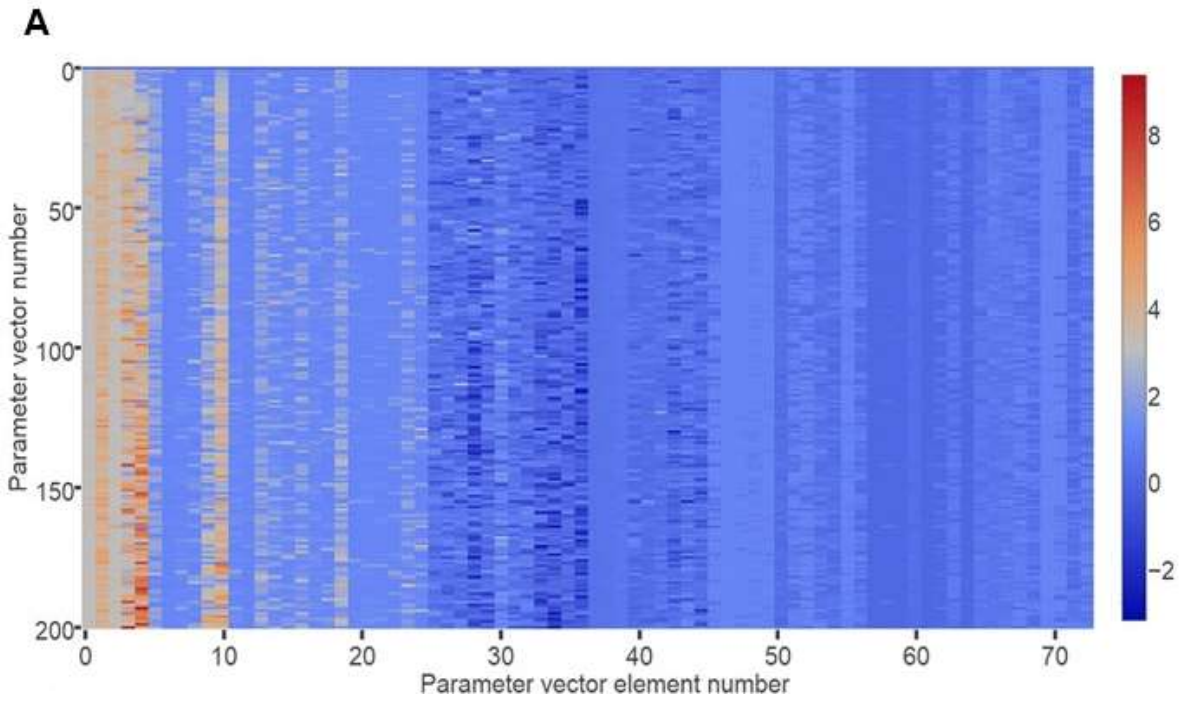
All training, pruning, enumeration of adjustable-TSC configurations with up to 6 possible adjustments, compiling of data into histograms and heatmaps, and FRIWA analysis was conducted in MATLAB with an Intel Core 2 Duo CPU processors with 2, 2.33 GHz cores and 4.00 GB of RAM under the Windows 7 operating system, an Intel-inside CORE i7 processor with 2, 2.69 GHz cores and 8.00 GB of RMA under the Windows 8 operating system, and an Intel Core i7 processor with 4, 4.00 GHz cores and 32.00 GB of RAM under the Windows 10 operating system Training a network (100 time steps, $1x10^6$ iterations, 99 training patterns) took between 30 and 35 minutes. Exhaustive enumeration of full sets of adjustable-TSC configurations to degree 6 took 1 minute. Computational overhead (limitations in computer memory) prevented computing the full set to level 7. Evaluating the degree of neuroadapation, neurotransmitter, and hormone levels of the full set of TSC-strength configurations to chronic drug or hormone combinations in each of the 3 representative networks took 17 minutes per network with MATLAB. Python was used for enumeration and storage of TSC-strength configurations for temporal-logic analysis. Python search and LTL analysis of TSC-strength configurations having 579,125 states took 4 minutes on one quad-core Intel Core i5 processor. After steady-state values had been cached, all subsequent

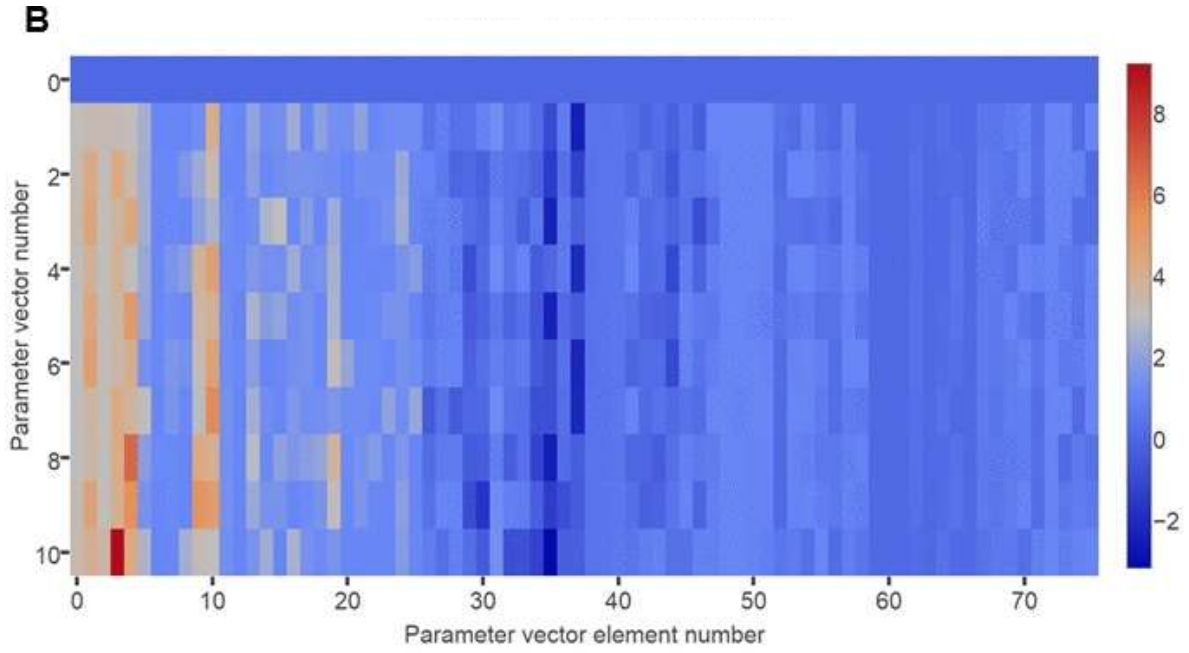
model checks took an average of 12 seconds. Python analysis was limited to 6 adjustments for consistency with the MATLAB analysis and because the LTL results were unlikely to be different for degree 7 than for degree 6.

APPENDIX C: RESULTS APPENDICES

C.1 ANALYSIS OF M-MODEL OPTIMIZED PARAMTER VECTORS

Before the M-model could be used for analysis of adapted TSC strength configurations, its parameters must be set so that model behavior agrees with experimental observations on the acute effects of antidepressants that occur before TSCs have adapted. The GA was used to obtain 200 sets of parameters that achieve this agreement with acute data by minimizing the RMS value of an error function. Panel A of the figure below is a heat map showing the parameter sets as parameter vectors, arranged with increasing Euclidian distance from a reference vector of all zeros. The RMS errors ranged between 5.66 and 18.45 and did not change systematically with distance from the reference vector. The heat map reveals no obvious sign of clustering, suggesting that the error function does not have multiple, widely separated minima.





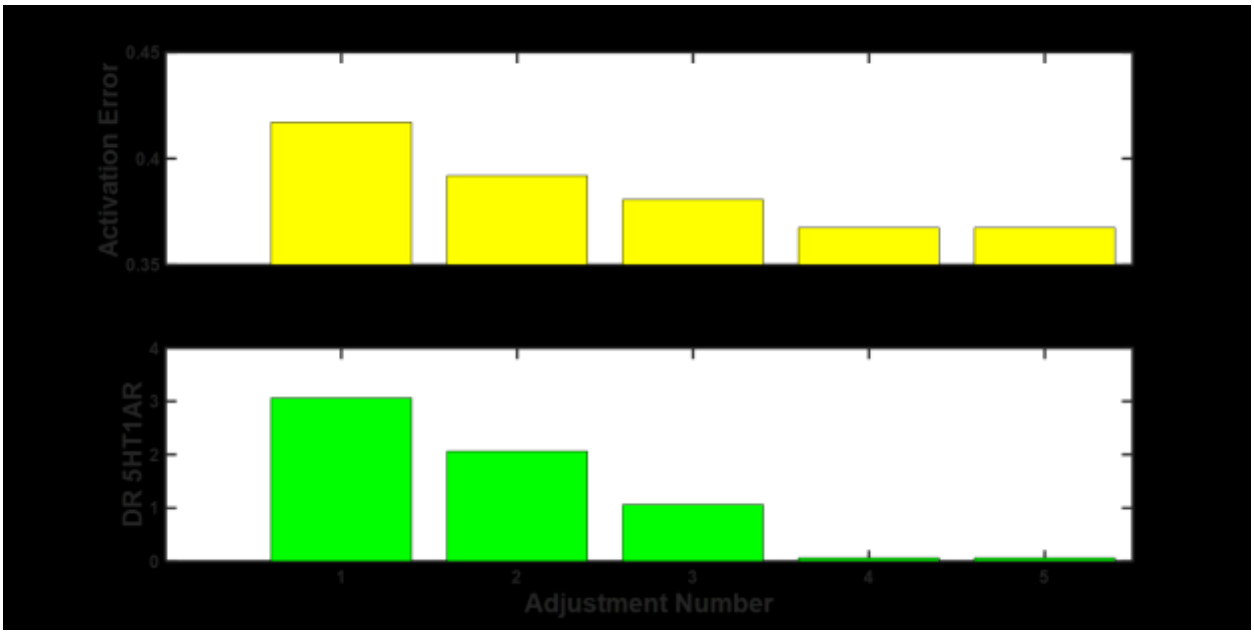
Panel B of the figure is a heat map showing the 10 best (lowest error) parameter vectors arranged with increasing Euclidian distance from the reference vector. The RMS errors ranged between 5.66 and 9.94. Again there is no obvious clustering. Of the 10 best fits, one was eliminated due to its aberrant adaptive behavior (see Results). The remaining nine parameterizations produced model instances that all had similar adaptive behavior that was also consistent with experimental observations. All elevated 5HT after acute Escitalopram administration (de Montigny, Chaput et al. 1990, El Mansari, Sanchez et al. 2005), all responded to acute Escitalopram with decreased DR unit activity (de Montigny, Chaput et al. 1990), and all elevated 5HT to an even higher level after adaptation to Escitalopram (de Montigny, Chaput et al. 1990, Invernizzi, Belli et al. 1992, El Mansari, Sanchez et al. 2005). When only the DR 5HT1A autoreceptor was allowed to adapt, all desensitized this receptor to reduce activation error (de Montigny, Chaput et al. 1990) (Naudon, El Yacoubi et al. 2002). The fit with the RMS error of 9.93 was selected for further analysis. It was considered representative because it had an error near the top of the error range but still displayed the required adaptive capability. The model with the representative parameter set was used in the generation of all M-model results.

C.2 VERIFYING AGREEMENT BETWEEN BETWEEN THE MATLAB AND MAUDE VERSIONS OF THE M-MODEL

To verify agreement between the MATLAB and Maude versions of the M-Model, the values of multiple variables were compared after the same number of time steps (150) in both programs. We found that the activity levels of all 6 units (DR, LC, VTA, tCRF, Tgal, Tglu) and levels of all of the neurotransmitters were in agreement between the 2 programs after 150 iterations to 4 significant places in the no-drug condition. We also verified that the 2 versions agreed on the effects of all drugs and combinations (Escitalopram, Nomifensine, Reboxetine, Trazodone, Asenapine, Aripiprazole, Bupropion, Quetiapine, Escitalopram/Aripiprazole, and Escitalopram/Quetiapine). We found agreement on the activity levels of all 6 units, levels of all of the neurotransmitters, and activation errors after 150 iterations to 4 significant places with acute administration (no-adaptation) of all of the drugs and combinations.

C.3 SINGLE-PATHWAY ADAPTATION RUNS IN MATLAB

Because the GA-determined values of the autoreceptor strengths of the M-model were all near 3 (3.10 for DR 5HT1A, 3.20 for LC AR2, and 3.20 for VTA D2R in the representative parameter set), DR 5HT1A autoreceptors could desensitize almost completely in 3 adjustment steps (3 adjustments down by 1) as part of simulated neuroadaptation. This is consistent with experimental observation on DR 5HT1A autoreceptor desensitization under chronic SSRI (Blier, Pineyro et al. 1998, Rainer, Nguyen et al. 2012). An example, short MATLAB adaptation run, out to five adjustments steps, is shown in the figure below.

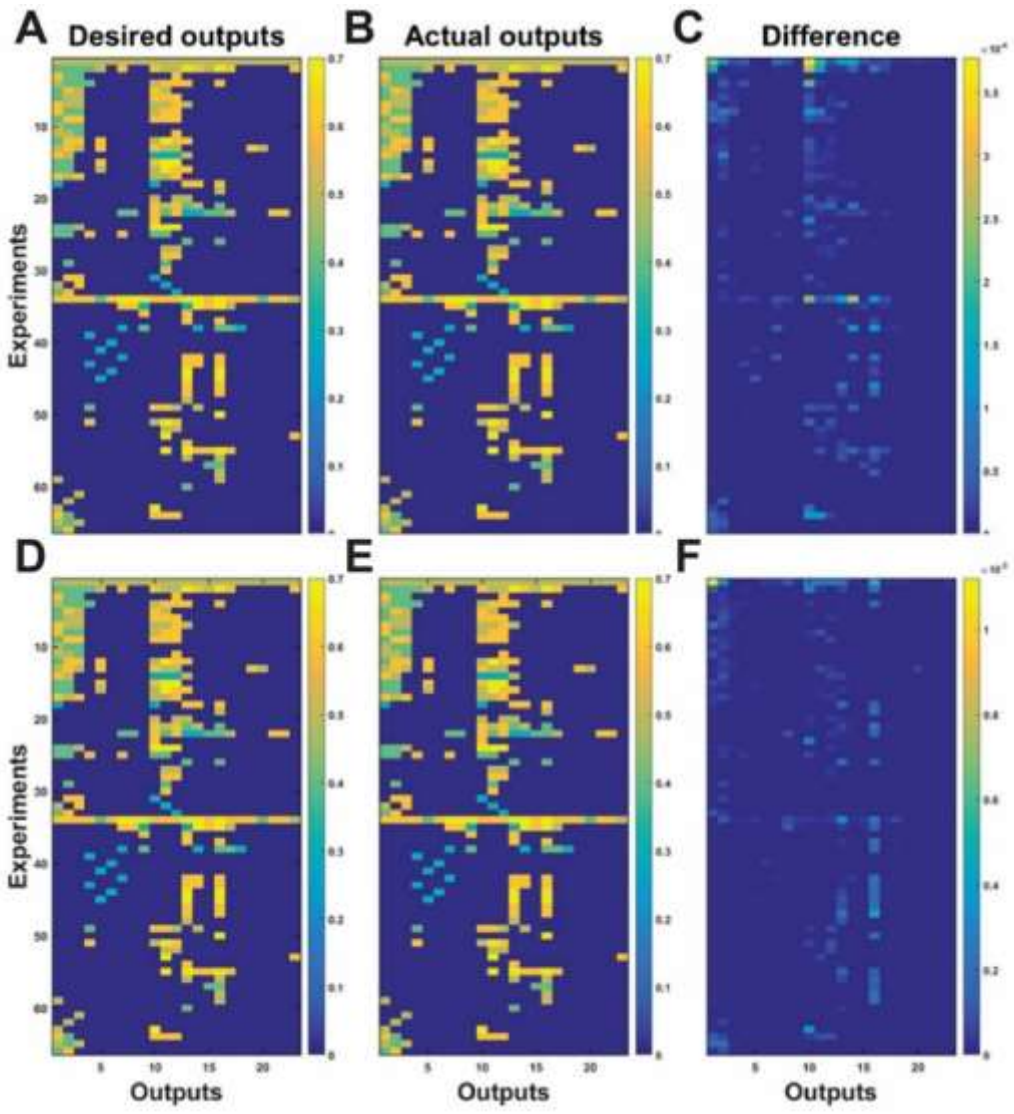


Neuroadaptation to chronic Escitalopram decreases activation error in the M-model, thereby bringing the activations of the monoaminergic units back towards their normative levels. In this single-sequence adaptation run, only the 5HT1A autoreceptor on the DR unit (the 5HT1A autoreceptor) was allowed to adapt. It could adjust its strength up or down by 1 on each of 5 adjustments, but the adjustment is retained only if it results in a decrease in activation error. The receptor decrements to 0 over adjustment steps 2, 3, and 4. No change occurs on adjustment step 1 because the randomly chosen adjustment was an increment, but that adjustment was rejected because it did not decrease activation error. Similarly, no change occurs on the last step because no further error-reducing adjustment can be made.

C.4 CLOSE AGREEMENT BETWEEN DESIRED (I.E. TARGET) AND ACTUAL OUTPUT RESPONSES AFTER TRAINING BUT BEFORE PRUNING (A-C) AND AFTER PRUNING AND RE-TRAINING (D-F) WITH MS- AND MSS-MODELS

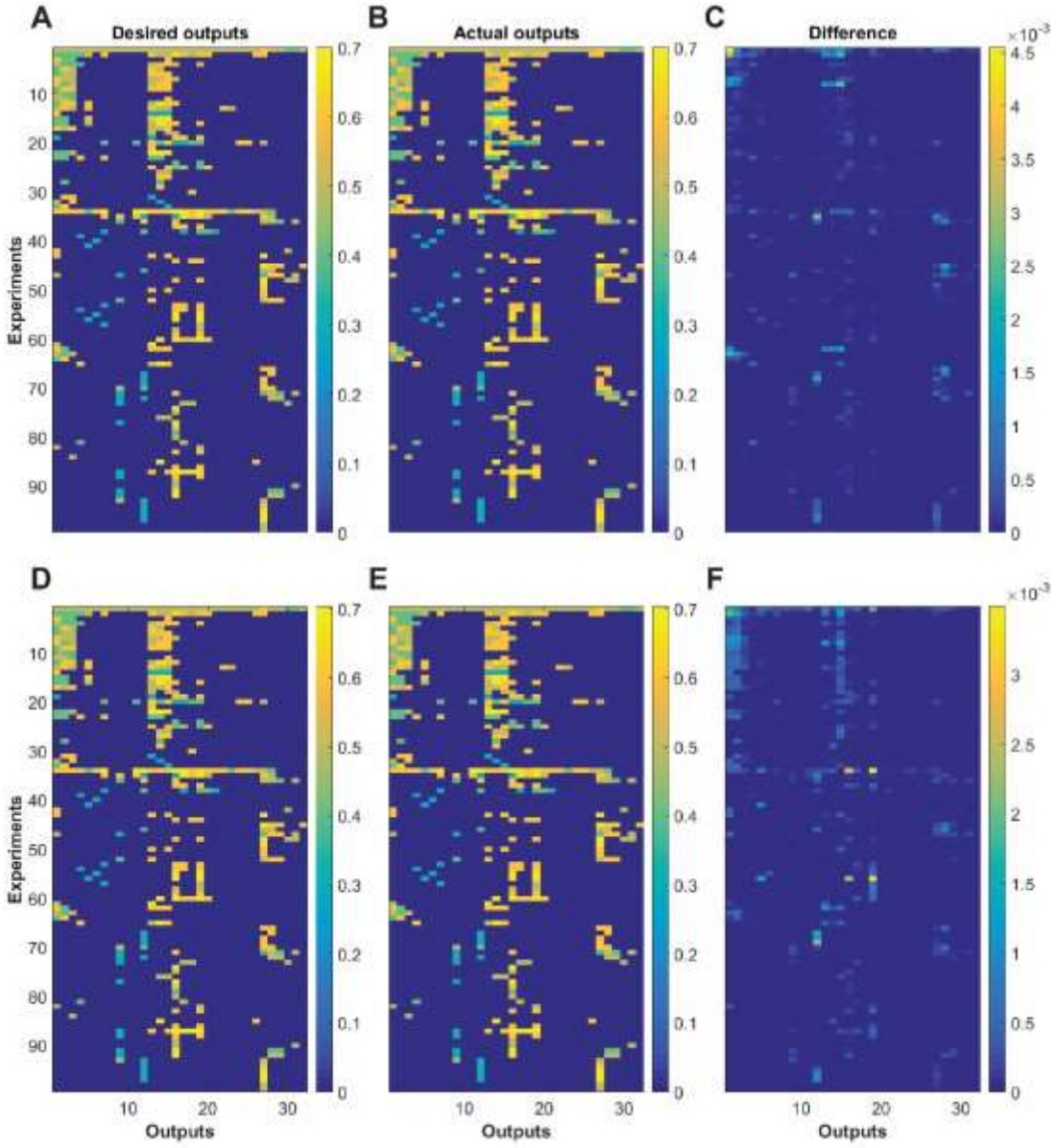
C.4.1 MS-MODEL

The colormap scales for the desired and actual output plots (A, B, D, and E) are the same, ranging from 0.00 to 0.70. Each row represents the same input pattern and each column represents an output value. The first row represents the no-drug baseline values. The colormap for the absolute differences or errors between the desired and actual outputs (C and F) are between the minimum and maximum absolute difference values for each plot, which is 0.00 to 3.77x10−4 for (C) and 0.00 to 1.10x10−3 for (F). Pruning was done to minimize non-structure connections. The RMS error over all training patterns was 2.39x10−5 for the unpruned network and 5.10x10−5 for the pruned and re-trained network.


A
Desired outputs
B
Actual outputs
C
Difference
D
E
F
Experiments
Outputs
Outputs
Outputs

C.4.2 MSS-MODEL

The colormap scales for the desired and actual output plots (A,B,C,D, and E) range from 0.00 to 0.70. Each row represents a single input pattern and each column represents an output value. The first row represents baseline output values when no inputs are present. The colormap for the absolute differences between the desired and actual output values (C and F) are between 0.00 and 4.50×10^{-3} for (C) and 0.00 and 3.50×10^{-3} for (F). The networks were pruned to minimize non-structure connections. The RMS error over all training patterns was 2.02×10^{-4} for the unpruned network in (A-C) and 1.84×10^{-4} for the pruned network in D-F.



APPENDIX D: DISCUSSION APPENDICES

D.1 POTENTIAL CLINICAL RELEVANCE OF M-MODEL RESULTS

The potential clinical relevance of the M-model results is evaluated on the basis of the idea that depression subtypes exist and can be categorized as psychotic or melancholic depression, or as heterogeneous, non-melancholic depressive disorder (Parker 2000). Patients with psychotic depression have consistently been found to respond to antidepressant drug combinations that chronically elevate DA levels, while patients with melancholic depression have shown considerable improvement with interventions that elevate NE levels (Spiker, Weiss et al. 1985, Parker, Roy et al. 1992, Guelfi, White et al. 1995, Kelly and Cooper 1997). Due to the finding that enhancing 5HT neurotransmission has been found to alleviate depressive symptomatology in patients with heterogeneous pathology not classically associated with either psychotic or melancholic depression, it has been proposed that serotonergic dysfunction may explain heterogeneous, non-melancholic depression (Malhi, Parker et al. 2002, Malhi, Parker et al. 2005).

Although we focus on SSRIs (e.g., Escitalopram), the M-model also provides potential insights into the clinical efficacies of some antidepressant drugs other than Escitalopram, and combinations of other drugs with Escitalopram. The selective NE and DA releaser Bupropion, for example, has been shown to be at least as effective as SSRIs in clinical studies (Thase, Haight et al. 2005, Papakostas, Montgomery et al. 2007). In the M-model, Bupropion does not therapeutically elevate 5HT in as high a percentage of adapted configurations as Escitalopram (24% for Bupropion alone, 29% for Escitalopram alone), but Bupropion therapeutically elevates both NE and DA in 96% of adapted TSC strength configurations. Thus, the M-model suggests that Escitalopram would be more effective in cases where 5HT alone is deficient (non-melancholic depression), but that Bupropion would be most effective in cases where NE or DA is deficient (melancholic and psychotic depressions, respectively). The M-model suggests that Escitalopram or Bupropion alone achieve their main therapeutic effects through elevation in 5HT, or NE and DA, respectively. This is consistent with observations that 5HT depletion, but not NE depletion, cause relapse following chronic Escitalopram and that NE depletion, but not 5HT depletion, cause relapse following chronic Bupropion (Cooper, Wang et al. 1994, Evans, Golshan et al. 2002).

The therapeutic efficacy of the combination of Escitalopram and Bupropion has not been rigorously studied with placebo controls, but some depressed patients that did not respond to SSRIs showed significant improvement with this combination (Leuchter, Lesser et al. 2008). In the M-

model, almost all TSC strength configurations adapted to chronic Escitalopram/Bupropion are associated with elevated levels of one or more of the monoamines, with all three monoamines elevated in 72% of these configurations. This finding offers the prediction that the combination of Escitalopram and Bupropion would exhibit high efficacy in patient populations comprising more than one depressive subtype.

Nomifensine was found to be an effective antidepressant before its use was discontinued due to the development of hemolytic anemia in patients (Brogden, Heel et al. 1979, Mueller-Eckhardt, Giers et al. 1988). Because 62% of adapted TSC strength configurations in the M-model therapeutically elevate all three monoamines with chronic Nomifensine, this drug could be efficacious in depressed patients deficient in any of the three monoamines. When Nomifensine and Escitalopram are combined, the monoamine profile we obtained from the M-model is very similar to Nomifensine by itself. This was expected because Nomifensine also targets the 5HT transporter (Brogden, Heel et al. 1979, Tatsumi, Groshan et al. 1997). The M-model therefore suggests that Nomifensine by itself would be an effective antidepressant, but the use of this drug clinically has been discontinued (Mueller-Eckhardt, Giers et al. 1988). Development of a drug with a mechanism of action similar to Nomifensine but with fewer side effects could be useful for a broader range of depressed patients.

Reboxetine has previously been shown to alleviate depressive symptomatology by elevating NE levels with chronic use, but these findings have been contested by a meta-analysis that includes unpublished clinical trials (Page and Lucki 2002, Page, Brown et al. 2003, Hajos, Fleishaker et al. 2004, Eyding, Lelgemann et al. 2010). When the M-model was allowed to adapt to Reboxetine, NE was the only monoamine that was significantly elevated, and reached therapeutic levels in 100% of adaptive configurations. This is in agreement with previous findings that chronic Reboxetine is associated with elevated NE levels (Hajos, Fleishaker et al. 2004). However, antidepressants acting selectively on one monoamine, such as Reboxetine, alleviate symptoms of depression in a limited percentage of patients (Kornstein, Li et al. 2009, Eyding, Lelgemann et al. 2010), suggesting that elevating NE alone may not be sufficient to alleviate depressive symptomatology in most depressed patients. The combination of Escitalopram and Reboxetine has been studied in clinical trials with limited placebo controls, and it was found that the combination reduced depressive symptomatology in some SSRI non-responders (Rubio, San et al. 2004). We hypothesize that this clinical outcome could result because combining

Escitalopram and Reboxetine increases the number of adapted states in which NE as well as 5HT levels are therapeutically elevated, providing relief to patients whose depression involves deficient NE and/or 5HT.

When the M-model adapted to chronic Trazodone, 10% of adapted configurations had elevated DA and 18% had elevated NE, suggesting that this drug should ameliorate depression in some cases. Trazodone has previously been shown to significantly improve depressive symptomatology over placebo in depressed patients (Cunningham, Borison et al. 1994, Weisler, Johnston et al. 1994). Some authors posit this occurs by improving sleep quality (Weisler, Johnston et al. 1994), suggesting that its antidepressant effect may be secondary to its anti-insomnia effect and may not directly involve monoamine elevation. The anti-insomnia effect is thought to be mediated by the effects of Trazodone on histamine receptors (Stahl 2009). Histamine was excluded from the M-model because it is not co-released by any monoaminergic neurons and because we found no evidence that histamine receptors adjust their levels with chronic antidepressant administration. Trazodone itself was included in our drug corpus because, as a multi-target drug, it affects the 5HT1A, AR1, and AR2 receptors as well as the serotonin reuptake transporter (SERT) (Krege, Goepel et al. 2000, Stahl 2009), which are represented in the initial model. Data on trazodone was included mainly to expand the dataset that was used to parameterize the M-model.

Asenapine and Aripiprazole are antipsychotic drugs that have not been studied by themselves in clinical studies of unipolar depression. Chronic administration of these drugs produce very few adapted configurations that are associated with therapeutically elevated levels of any of the monoamines in the M-model, suggesting that Asenapine or Aripiprazole, administered by themselves, would not be clinically effective for depressed patients. In the M-model, 56% of TSC strength configurations adapted to chronic, combined Escitalopram and Asenapine were associated with therapeutically elevated NE levels. The clinical efficacy of the combination of Escitalopram and Asenapine in depression has not yet been studied, and the M-model suggests that this combination may have significant therapeutic efficacy in patients whose depression involves deficiencies in NE. The combination of Escitalopram and Aripiprazole therapeutically elevated 5HT levels in 36% of adapted TSC strength configurations in the M-model, which is somewhat higher than the 29% found with Escitalopram by itself. The M-model also found that 17% of configurations adapted to the combination of Escitalopram and Aripiprazole elevate both 5HT and DA, whereas no configurations adapted to Escitalopram alone

elevate DA. This modeling result suggests that the combination of Escitalopram and Aripiprazole may help alleviate depressive symptomatology in patients whose depression involves deficiencies in either 5HT or DA, and agrees with findings that this combination is effective in some depressed patients who do not respond to SSRIs (Marcus, McQuade et al. 2008, Matthews, Siefert et al. 2009, Boulton, Balch et al. 2010, Han, Wang et al. 2013).

Quetiapine (an antipsychotic) by itself has recently been shown to ameliorate depressive symptomatology in some patients in its extended release form (Cutler, Montgomery et al. 2009). In the M-model, Quetiapine does not therapeutically elevate 5HT in any configuration, but it does therapeutically elevate NE in all adapted configurations. Importantly, one of the observed effects of Quetiapine is to elevate DA levels (Werkman, Olijslagers et al. 2004). Only 9% of the receptor configurations adapted to Quetiapine by itself elevated DA to therapeutic levels in the M-model, suggesting that Quetiapine by itself can ameliorate depressive symptomatology in cases where NE is deficient and in some cases where DA is deficient. Although studies to date have not had adequate controls, the combination of an SSRI and Quetiapine appears to afford some improvement in patients that did not respond to SSRIs (Adson, Kushner et al. 2004, Baune, Caliskan et al. 2007). When the M-model adapted to chronic Escitalopram/Quetiapine, 100% of adapted configurations elevate NE to therapeutic levels, 34% elevate DA to therapeutic levels, and 11% elevate 5HT to therapeutic levels. The M-model found that 34% of adapted TSC strength configurations had therapeutic elevations in both DA and NE. This combination could be effective in depressive subtypes that involve a deficiency of DA and NE, and in some cases where 5HT is deficient.

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