

# Depression & Anxiety

## Clinical features, treatment, neurobiology & theory

Quentin J.M. Huys<sup>1,2</sup> and Klaas Enno Stephan<sup>1</sup>

1 Translational Neuromodeling Unit, Department of Biomedical Engineering, ETHZ and UZH

2 Department of Psychiatry, Psychosomatics and Psychotherapy, Psychiatric University Hospital, Zürich

**Organisers:**

Dr. Dr. Quentin Huys, huysq@ethz.ch

Prof. Dr. Dr. Klaas Stephan, stephan@biomed.ee.ethz.ch

TA: Daniel Renz, renz@biomed.ee.ethz.ch

PA: Silvia Princz, sprincz@biomed.ee.ethz.ch

website: [quentinhuys.com/teaching.html](http://quentinhuys.com/teaching.html)

Official: TNU and ETHZ

**Description:** Depression and anxiety disorders are amongst the most prominent psychiatric disorders in the world, and account for a disproportionately large fraction of the burden of psychiatric disease. The aim of the course is to give students a contemporary overview over anxiety and depression. The course will start by describing the clinical features, epidemiology and treatments. Substantial time will be devoted to animal models, human cognitive and neurobiological features and computational approaches.

**Where & when:** The course takes place on Friday afternoons from 14.00-16.00 in room ETZ F 91 (on Gloriastrasse) during the winter semester 2013/2014. Each session will contain a lecture followed by a journal club.

Please read both the **background reading** and the **journal club** paper, as these will be discussed in depth during the lecture.

**Credit:** To receive credit points, you must

- **either** give a 45min presentation in one of the seminar sessions covering all but the 'additional reading' papers. You may choose to either moderate the journal club, or to discuss the journal club paper in your talk. Moderating a journal club alone is insufficient.
- **or** program your own simulation addressing one of the topics discussed in the seminar and give a short presentation (5-10 min) of your code and results in the final session of the seminar. Papers marked in **red** might be most interesting for modelling projects.

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### 27.9 TOPIC & PAPER DISTRIBUTION

Please have a look at the course requirements and choose which, if any, sessions you would like to present.

## ANXIETY (4.10. - 18.10.)

### 4.10. BACKGROUND READING AND TREATMENTS

**Presenter** Background + JC: Eduardo Aponte

#### Background reading

- Shorter Oxford Textbook of Psychiatry, chapter 9 Anxiety disorders
- Ehlers and Clark (2000): A cognitive model of posttraumatic stress disorder.

#### Journal club

- Lamers et al. (2011): Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA).

#### Additional reading

- Stahl's Essential Psychopharmacology. Chapter 9: Anxiety disorders and anxiolytics
- Kaplan & Sadock: Synopsis of psychiatry, chapter 16 Anxiety disorders
- Clark et al. (2006): Cognitive therapy versus exposure and applied relaxation in social phobia: a randomized controlled trial.
- Oler et al. (2010): Amygdalar and hippocampal substrates of anxious temperament differ in their heritability
- Grupe and Nitschke (2013): Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective.
- Bach and Dolan (2012): Knowing how much you don't know: a neural organization of uncertainty estimates.

### 11.10. FEAR CONDITIONING AND EXTINCTION

**Presenter** Background + JC: Valance Wang

#### Background reading

- Bouton (2006): Chapter 3: The nuts and bolts of conditioning.
- LeDoux (2000): Emotion circuits in the brain.
- Schiller et al. (2010): Preventing the return of fear in humans using reconsolidation update mechanisms.

#### Journal club

- Gershman and Niv (2012): *Exploring a latent cause theory of classical conditioning.*

#### Additional reading

- Rogan et al. (1997): Fear conditioning induces associative long-term potentiation in the amygdala.
- Otto et al. (2010): Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder.
- Robinson et al. (2012): Acute tryptophan depletion increases translational indices of anxiety but not fear: serotonergic modulation of the bed nucleus of the stria terminalis?
- Li et al. (2011): *Differential roles of human striatum and amygdala in associative learning.*

### 18.10. OBSESSIVE-COMPULSIVE DISORDER

**Presenter**

Background: Dr. Frederike Petzschner

JC: Saeed Paliwal?

#### Background reading

- Shorter Oxford Textbook of Psychiatry, chapter 9 Anxiety disorders (part on OCD)
- Rotge et al. (2008): *A challenging task for assessment of checking behaviors in obsessive-compulsive disorder.*

**Journal club**

- Gillan et al. (2011): Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder

**Additional reading**

- Kaplan & Sadock: Synopsis of psychiatry, chapter 16 Anxiety disorders (part on OCD)
- Gillan et al. (2013): **Enhanced Avoidance Habits in Obsessive-Compulsive Disorder**
- Rotge et al. (2012): Forgetting what you have checked: a link between working memory impairment and checking behaviors in obsessive-compulsive disorder.

## DEPRESSION (25.10. AND 15.11.)

### 25.10. SYMPTOMS, SIGNS, EPIDEMIOLOGY & BIOLOGY

#### Presenter

Background: Dr. Helene Haker

JC: Tina Wentz

#### Background reading

- Shorter Oxford Textbook of Psychiatry, chapter 11 Mood disorders
- Kendler et al. (2000): Stressful Life Events and Previous Episodes in the Etiology of Major Depression in Women: An Evaluation of the “Kindling” Hypothesis
- Brown (1993): Life events and affective disorder: replications and limitations

#### Journal club

- Kendler et al. (1999): Causal Relationship Between Stressful Life Events and the Onset of Major Depression

#### Additional reading

- Kaplan & Sadock: Synopsis of psychiatry, chapter 15 Mood disorders
- William Styron: Darkness Visible. A memoir of madness.
- Wittchen et al. (2003): Depressive episodes—evidence for a causal role of primary anxiety disorders?

### 1.11. NEUROBIOLOGY OF DEPRESSION

Presenter Background + JC: Laura Bohleber

#### Background reading

- Drevets et al. (2008): The subgenual anterior cingulate cortex in mood disorders.
- Krishnan and Nestler (2008): The molecular neurobiology of depression.

#### Journal club

- Drevets et al. (1997): Subgenual prefrontal cortex abnormalities in mood disorders

#### Additional reading

- Mayberg (1997): **Limbic-cortical dysregulation: a proposed model of depression.**
- Heim et al. (2000): Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood.

### 8.11. ANHEDONIA AND REWARD

Presenter Background + JC: Suraj Honnuraiah

#### Background reading

- Eshel and Roiser (2010): Reward and punishment processing in depression.
- Treadway and Zald (2011): Reconsidering anhedonia in depression: lessons from translational neuroscience.
- Bylsma et al. (2008): A meta-analysis of emotional reactivity in major depressive disorder.

#### Journal club

- Tye et al. (2013): Dopamine neurons modulate neural encoding and expression of depression-related behaviour.

#### Additional reading

- Pizzagalli et al. (2005): **Toward an objective characterization of an anhedonic phenotype: a signal-detection approach.**
- Huys et al. (2013): **Mapping anhedonia onto reinforcement learning: A behavioural meta-analysis.**
- Rottenberg et al. (2005): Emotion context insensitivity in major depressive disorder.

## 15.11. THE TREATMENT OF DEPRESSION

### Presenter

Background: Prof. Dr. Heinz Böker

JC: Quentin Huys

### Background reading

- Pharmacological: Stahl's essential psychopharmacology, chapter 11
- Cognitive: Disner et al. (2011): Neural mechanisms of the cognitive model of depression.
- Neurosurgical: Andrade et al. (2010): Neurostimulatory and ablative treatment options in major depressive disorder: a systematic review

### Journal club

- Rush et al. (2006): Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report.

### Additional reading

- Geddes et al. (2003): Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review.
- Mayberg et al. (2005): Deep Brain Stimulation for Treatment-Resistant Depression

## COGNITION & NEUROBIOLOGY OF DEPRESSION & ANXIETY (22.11. - 13.12.)

### 22.11: ATTENTION, EMOTION AND MEMORY IN DEPRESSION & ANXIETY

**Presenter** Background + JC: Konstantinos Zeimpekis

#### Background reading

- Gotlib and Joormann (2010): Cognition and depression: current status and future directions.
- Mathews and MacLeod (2005): Cognitive vulnerability to emotional disorders.
- Williams et al. (2007): Autobiographical Memory Specificity and Emotional Disorder

#### Journal club

- Harlé et al. (2013): **The influence of emotions on cognitive control: Feelings and beliefs – where do they meet?**

#### Additional reading

- MacLeod et al. (1986): Attentional bias in emotional disorders.
- Gotlib et al. (2004): Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression

### 29.11. SEROTONIN IN DEPRESSION & ANXIETY

**Presenter** Background + JC: Caroline Jahn

#### Background reading

- Ruhé et al. (2007): Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies.
- Karg et al. (2011): The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation.
- Best et al. (2011): **Bursts and the efficacy of selective serotonin reuptake inhibitors.**
- Harmer et al. (2009): Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action.

#### Journal club

- Caspi et al. (2003): Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene

#### Additional reading

- Parsey et al. (2006): Lower serotonin transporter binding potential in the human brain during major depressive episodes.
- Lanzenberger et al. (2012): Prediction of SSRI treatment response in major depression based on serotonin transporter interplay between median raphe nucleus and projection areas.
- Harmer et al. (2004): Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition.
- Smith et al. (1997): Relapse of depression after rapid depletion of tryptophan

### 6.12. HELPLESSNESS

**Presenter** Background + JC: Kate Lomakina

#### Background reading

- Maier et al. (2006): Behavioral control, the medial prefrontal cortex, and resilience.
- Willner (2005): Chronic Mild Stress (CMS) Revisited: Consistency and Behavioural-Neurobiological Concordance in the Effects of CMS
- Alloy et al. (1999): Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins.

### Journal club

- Amat et al. (2005): Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus.

### Additional reading

- Huys and Dayan (2009): [A Bayesian formulation of behavioral control.](#)
- Warden et al. (2012): A prefrontal cortex-brainstem neuronal projection that controls response to behavioural challenge.
- Haefffel et al. (2007): A preliminary test of a dual-process theory of cognitive vulnerability to depression.

## 13.12. COGNITIVE CONTROL

**Presenter** Background + JC: Daniel Renz

### Background reading

- Gross (2002): Emotion regulation: affective, cognitive, and social consequences.
- Ochsner and Gross (2005): The cognitive control of emotion.
- Roiser et al. (2009): [A Genetically Mediated Bias in Decision Making Driven by Failure of Amygdala Control.](#)
- Pezawas et al. (2005): 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression.
- Heinz et al. (2005): Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter.

### Journal club

- Lee et al. (2012): Amygdala-prefrontal coupling underlies individual differences in emotion regulation.

### Additional reading

- Erk et al. (2010): Acute and sustained effects of cognitive emotion regulation in major depression.
- Johnstone et al. (2007): Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression.

## 20.12. FINAL EXAMINATION SESSION

10-min slots will be reserved for all those who programmed their own simulation addressing one of the topics discussed in the seminar. They will give a short presentation (5-10 min) of their code and results in the final session of the seminar.

## EXERCISE: OPTION 1

In this exercise, you will be asked to code up a simple reinforcement-learning agent, and then to infer from observed behaviour what its learning parameters were. A reference book is Sutton and Barto (1998), and a brief overview set of slides is at <http://quentinhuy.com/pub/Huys13-ACCN-RL-Theory.pdf>.

### GENERATING DATA

Consider a simple experiment like that in Pizzagalli et al. (2005), in which subjects are faced with a set of stimuli  $s \in \mathcal{S}$ , and for each stimulus have to choose one of a set of actions  $a \in \mathcal{A}$ . For each stimulus, a different action  $a$  is rewarded, i.e. if the subject chooses that action, then they receive a reward of size  $\rho$  with probability  $p(r; s, a)$ , and otherwise no reward.

Consider now a simple Rescorla-Wagner-like learning model (Rescorla and Wagner, 1972). Agents are presented with a known sequence of stimuli, with stimulus  $s_t$  being presented on trial  $t$ . On each trial  $t$ , an agent chooses between one of two actions  $a_t \in \{0, 1\}$  according to a probability

$$p(a_t) = \frac{e^{Q_t(a_t, s_t)}}{\sum_{a'} e^{Q_t(a', s_t)}} \quad (1)$$

where  $Q_t(a_t, s_t)$  is the expected value of emitting action  $a_t$  in the presence of  $s_t$ . It is an exponentially weighted average of past rewards which is updated, on each trial  $t$  on which action  $a_t$  is taken in the presence of stimulus  $s_t$  as

$$Q_t(a_t, s_t) = Q_{t-1}(a_t, s_t) + \alpha(\rho r_t - Q_{t-1}(a_t, s_t)) \quad (2)$$

where  $r_t$  equals unity on trials on which a reward (of size  $\rho$ ) was obtained, and 0 on other trials. The parameter  $\alpha$  is the so-called 'learning rate'.

First, assume there is only one stimulus and one action.

**Part 1:** Show analytically that for small  $\alpha$ ,  $Q$  tends asymptotically towards  $p(r; s)\rho$ .

**Part 2:** Derive analytically the mean and variance of the distribution of  $Q_t$ , given known values of  $\alpha$ ,  $\rho$  and  $p(r; s)$ . Assume  $Q_0 = 0$ . Note that the moment generating function for a Bernoulli random variable with probability  $p$  is  $p + (1 - p)e^t$ .

**Part 3:** Generate a random sequence of length 300 by flipping a coin with probability 0.5. Let 0 indicate that stimulus 1 was presented, and 1 indicate stimulus 2. Generate a sequence of choices  $a_t$  with  $\rho = 2$ ,  $\alpha = 0.2$  and  $p(r = 1; s_1, a_1) = 0.8$ ,  $p(r = 1; s_1, a_2) = 0.2$ ,  $p(r = 1; s_2, a_1) = 0.2$  and  $p(r = 1; s_2, a_2) = 0.8$ . Generate a plot of showing how the distribution of  $Q$  for the two actions, and the choice behaviour itself evolves.

### INFERRING THE PARAMETERS

From the choice data you just generated, you will now infer the parameters  $\rho$  and  $\alpha$ . Assume the outcome probabilities  $p(r; s, a)$  are known and  $Q_0 = 0$ .

**Part 4:** Given the probability of choices in equation 1, write down the total log likelihood of the entire sequence of choices.

**Part 5:** Maximise this log likelihood with respect to the parameters  $\alpha$  and  $\rho$ . You may choose gradient ascent, or any other method of your liking. Show that you are able to recover the true parameters used to generate the data.

### ANHEDONIA AND LEARNING IMPAIRMENTS

A key component of depression is anhedonia, a subjective sense that what used to be pleasurable no longer is. Tasks like that by Pizzagalli et al. (2005) have been used to try to measure anhedonia directly without having to rely on conscious verbal reports.



Also read Schultz et al. (1997). This paper argues that dopaminergic neurons in the ventral tegmental area of the midbrain report the learning signal  $\delta_t = r_t - Q(a_t, s_t)$ .

**Part 6:** Generate some more datasets of choices and run the inference again. What do you notice about your inference of  $\alpha$  and  $\rho$ ?

**Part 7:** Would anhedonia best be captured by  $\alpha$  or  $\rho$ ? Explain your reasoning. If dopamine reports the prediction error as suggested by Schultz et al. (1997), which parameter would a dysfunction of the dopaminergic system most likely affect?

**Part 8 - not compulsory:** design a task to optimize the ability of distinguishing between  $\alpha$  and  $\rho$ .

### SUBMISSION OPTION 1

Please submit one archive containing:

- one pdf file with the answers to the questions and with graphs showing the results of the simulations.
- The code in matlab. It should be ready to run and produce all relevant figures without further input.

### EXERCISE: OPTION 2

Alternatively, you can develop your own model of one of the papers highlighted in red. This should be a mathematical model, with simulations in matlab.

### SUBMISSION OPTION 2

Please submit one archive containing:

- one pdf file with the description of your question, the model, and the results.
- The code in matlab. It should be ready to run and produce all relevant figures without further input.

## REFERENCES

- Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Tashman, N. A., Steinberg, D. L., Rose, D. T., and Donovan, P. (1999). Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. *Behav Res Ther*, 37(6):503–531.
- Amat, J., Baratta, M. V., Paul, E., Bland, S. T., Watkins, L. R., and Maier, S. F. (2005). Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nat. Neurosci.*, 8(3):365–71.
- Andrade, P., Noblesse, L. H. M., Temel, Y., Ackermans, L., Lim, L. W., Steinbusch, H. W. M., and Visser-Vandewalle, V. (2010). Neurostimulatory and ablative treatment options in major depressive disorder: a systematic review. *Acta Neurochir (Wien)*, 152(4):565–577.
- Bach, D. R. and Dolan, R. J. (2012). Knowing how much you don't know: a neural organization of uncertainty estimates. *Nat Rev Neurosci*, 13(8):572–586.
- Best, J., Nijhout, H. F., and Reed, M. (2011). Bursts and the efficacy of selective serotonin reuptake inhibitors. *Pharmacopsychiatry*, 44 Suppl 1:S76–S83.
- Bouton, M. E. (2006). *Learning and Behavior: A Contemporary Synthesis*. Sinauer, USA.
- Brown, G. W. (1993). Life events and affective disorder: replications and limitations. *Psychosom Med*, 55(3):248–259.
- Bylsma, L. M., Morris, B. H., and Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clin Psychol Rev*, 28(4):676–691.
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, W., McClay, J., Mill, J., Martin, J., Braithwaite, A., and Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT genes. *Science*, 301:386–89.
- Clark, D. M., Ehlers, A., Hackmann, A., McManus, F., Fennell, M., Grey, N., Waddington, L., and Wild, J. (2006). Cognitive therapy versus exposure and applied relaxation in social phobia: a randomized controlled trial. *Journal of Consulting and Clinical Psychology*, 74(3):568.
- Disner, S. G., Beevers, C. G., Haigh, E. A. P., and Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci*, 12(8):467–477.
- Drevets, W. C., Price, J. L., Simpson, J. R., Todd, R. D., Reich, T., Vannier, M., and Raichle, M. E. (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, 386:824–7.
- Drevets, W. C., Savitz, J., and Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectr*, 13(8):663–681.
- Ehlers, A. and Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour research and therapy*, 38(4):319–345.
- Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., and Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *J Neurosci*, 30(47):15726–15734.
- Eshel, N. and Roiser, J. P. (2010). Reward and punishment processing in depression. *Biol Psychiatry*, 68(2):118–124.
- Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., and Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*, 361(9358):653–661.
- Gershman, S. J. and Niv, Y. (2012). Exploring a latent cause theory of classical conditioning. *Learn Behav*, 40(3):255–268.
- Gillan, C. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Voon, V., Apergis-Schoute, A. M., Fineberg, N. A., Sahakian, B. J., and Robbins, T. W. (2013). Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry*.
- Gillan, C. M., Pappmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., and de Wit, S. (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry*, 168(7):718–726.
- Gotlib, I. H. and Joormann, J. (2010). Cognition and depression: current status and future directions. *Annu Rev Clin Psychol*, 6:285–312.
- Gotlib, I. H., Krasnoperova, E., Yue, D. N., and Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *J Abnorm Psychol*, 113(1):121–135.
- Gross, J. J. (2002). Emotion regulation: affective, cognitive, and social consequences. *Psychophysiology*, 39(3):281–291.

- Grupe, D. W. and Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nat Rev Neurosci*, 14(7):488–501.
- Haefffel, G. J., Abramson, L. Y., Brazy, P. C., Shah, J. Y., Teachman, B. A., and Nosek, B. A. (2007). Explicit and implicit cognition: a preliminary test of a dual-process theory of cognitive vulnerability to depression. *Behav Res Ther*, 45(6):1155–1167.
- Harlé, K. M., Shenoy, P., and Paulus, M. P. (2013). The influence of emotions on cognitive control: Feelings and beliefs – where do they meet? *Frontiers in Human Neuroscience*, 7(508).
- Harmer, C. J., Goodwin, G. M., and Cowen, P. J. (2009). Why do antidepressants take so long to work? a cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry*, 195(2):102–108.
- Harmer, C. J., Shelley, N. C., Cowen, P. J., and Goodwin, G. M. (2004). Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry*, 161(7):1256–1263.
- Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., Miller, A. H., and Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*, 284(5):592–7.
- Heinz, A., Braus, D. F., Smolka, M. N., Wrase, J., Puls, I., Hermann, D., Klein, S., Grusser, S. S. M., Flor, H., Schumann, G., Mann, K., and Buchel, C. (2005). Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat Neurosci*, 8(1):20–1.
- Huys, Q. J. M. and Dayan, P. (2009). A bayesian formulation of behavioral control. *Cognition*, 113(3):314–328.
- Huys, Q. J. M., Pizzagalli, D. A., Bogdan, R., and Dayan, P. (2013). Mapping anhedonia onto reinforcement learning: A behavioural meta-analysis. *Biol Mood Anxiety Disord*, 3(1):12.
- Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., and Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci*, 27(33):8877–8884.
- Karg, K., Burmeister, M., Shedden, K., and Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psychiatry*, 68(5):444–454.
- Kendler, K. S., Karkowski, L. M., and Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatry*, 156:837–41.
- Kendler, K. S., Thornton, L. M., and Gardner, C. O. (2000). Stressful life events and previous episodes in the etiology of major depression in women: An evaluation of the “kindling” hypothesis. *Am. J. Psychiatry*, 157:1243–51.
- Krishnan, V. and Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, 455(7215):894–902.
- Lamers, F., van Oppen, P., Comijs, H. C., Smit, J. H., Spinhoven, P., van Balkom, A. J. L. M., Nolen, W. A., Zitman, F. G., Beekman, A. T. F., and Penninx, B. W. J. H. (2011). Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the netherlands study of depression and anxiety (nesda). *J Clin Psychiatry*, 72(3):341–348.
- Lanzenberger, R., Kranz, G. S., Haeusler, D., Akimova, E., Savli, M., Hahn, A., Mitterhauser, M., Spindelegger, C., Philippe, C., Fink, M., Wadsak, W., Karanikas, G., and Kasper, S. (2012). Prediction of ssri treatment response in major depression based on serotonin transporter interplay between median raphe nucleus and projection areas. *Neuroimage*, 63(2):874–881.
- LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu Rev Neurosci*, 23:155–184.
- Lee, H., Heller, A. S., van Reekum, C. M., Nelson, B., and Davidson, R. J. (2012). Amygdala-prefrontal coupling underlies individual differences in emotion regulation. *Neuroimage*, 62(3):1575–1581.
- Li, J., Schiller, D., Schoenbaum, G., Phelps, E. A., and Daw, N. D. (2011). Differential roles of human striatum and amygdala in associative learning. *Nat Neurosci*, 14(10):1250–1252.
- MacLeod, C., Mathews, A., and Tata, P. (1986). Attentional bias in emotional disorders. *J Abnorm Psychol*, 95(1):15–20.
- Maier, S. F., Amat, J., Baratta, M. V., Paul, E., and Watkins, L. R. (2006). Behavioral control, the medial prefrontal cortex, and resilience. *Dialogues Clin Neurosci*, 8(4):397–406.
- Mathews, A. and MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol*, 1:167–195.
- Mayberg, H., Lozano, A., Voon, V., McNeely, H., Seminowicz, D., Hamani, C., Schwab, J.,

- and Kennedy, S. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, 45(5):651–60.
- Mayberg, H. S. (1997). Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsych.*, 9(3):471–81.
- Ochsner, K. N. and Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci*, 9(5):242–249.
- Oler, J. A., Fox, A. S., Shelton, S. E., Rogers, J., Dyer, T. D., Davidson, R. J., Shelledy, W., Oakes, T. R., Blangero, J., and Kalin, N. H. (2010). Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. *Nature*, 466(7308):864–868.
- Otto, M. W., Tolin, D. F., Simon, N. M., Pearlson, G. D., Basden, S., Meunier, S. A., Hofmann, S. G., Eisenmenger, K., Krystal, J. H., and Pollack, M. H. (2010). Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry*, 67(4):365–370.
- Parsey, R. V., Hastings, R. S., Oquendo, M. A., Yu Huang, Y., Simpson, N., Arcement, J., Huang, Y., Ogden, R. T., Heertum, R. L. V., Arango, V., and Mann, J. J. (2006). Lower serotonin transporter binding potential in the human brain during major depressive episodes. *Am J Psychiatry*, 163(1):52–58.
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., Egan, M. F., Mattay, V. S., and Weinberger, A. R. H. D. R. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat. Neurosci.*, 8(6):828–34.
- Pizzagalli, D. A., Jahn, A. L., and O’Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol Psychiatry*, 57(4):319–327.
- Rescorla, R. and Wagner, A. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical conditioning II: Current research and theory*, pages 64–99.
- Robinson, O. J., Overstreet, C., Allen, P. S., Pine, D. S., and Grillon, C. (2012). Acute tryptophan depletion increases translational indices of anxiety but not fear: serotonergic modulation of the bed nucleus of the stria terminalis? *Neuropsychopharmacology*, 37(8):1963–1971.
- Rogan, M. T., Stubli, U. V., and LeDoux, J. E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature*, 390(6660):604–607.
- Roiser, J. P., de Martino, B., Tan, G. C. Y., Kumaran, D., Seymour, B., Wood, N. W., and Dolan, R. J. (2009). A genetically mediated bias in decision making driven by failure of amygdala control. *J Neurosci*, 29(18):5985–5991.
- Rotge, J. Y., Clair, A. H., Jaafari, N., Hantouche, E. G., Pelissolo, A., Goillandeau, M., Pochon, J. B., Guehl, D., Bioulac, B., Burbaud, P., Tignol, J., Mallet, L., and Aouizerate, B. (2008). A challenging task for assessment of checking behaviors in obsessive-compulsive disorder. *Acta Psychiatr Scand*, 117(6):465–473.
- Rotge, J.-Y., Langbour, N., Dilharreguy, B., Bordessoulles, M., Guehl, D., Bioulac, B., Martin-Guehl, C., Jaafari, N., Aouizerate, B., Allard, M., and Burbaud, P. (2012). Contextual and behavioral influences on uncertainty in obsessive-compulsive disorder. *Cortex*.
- Rottenberg, J., Gross, J. J., and Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *J Abnorm Psychol*, 114(4):627–639.
- Ruhé, H. G., Mason, N. S., and Schene, A. H. (2007). Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry*, 12(4):331–359.
- Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., and Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a star\*d report. *Am J Psychiatry*, 163(11):1905–1917.
- Schiller, D., Monfils, M.-H., Raio, C. M., Johnson, D. C., Ledoux, J. E., and Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, 463(7277):49–53.
- Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, 275(5306):1593–1599.
- Smith, K. A., Fairburn, C. G., and Cowen, P. J. (1997). Relapse of depression after rapid depletion of tryptophan. *Lancet*, 249:915–9.

- Sutton, R. S. and Barto, A. G. (1998). *Reinforcement Learning: An Introduction*. MIT Press, Cambridge, MA.
- Treadway, M. T. and Zald, D. H. (2011). Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*, 35(3):537–555.
- Tye, K. M., Mirzabekov, J. J., Warden, M. R., Ferenczi, E. A., Tsai, H.-C., Finkelstein, J., Kim, S.-Y., Adhikari, A., Thompson, K. R., Andalman, A. S., Gunaydin, L. A., Witten, I. B., and Deisseroth, K. (2013). Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*, 493(7433):537–541.
- Warden, M. R., Selimbeyoglu, A., Mirzabekov, J. J., Lo, M., Thompson, K. R., Kim, S.-Y., Adhikari, A., Tye, K. M., Frank, L. M., and Deisseroth, K. (2012). A prefrontal cortex-brainstem neuronal projection that controls response to behavioural challenge. *Nature*, 492(7429):428–432.
- Williams, J. M. G., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., and Dalgleish, T. (2007). Autobiographical memory specificity and emotional disorder. *Psychol Bull*, 133(1):122–148.
- Willner, P. (2005). Chronic mild stress (cms) revisited: Consistency and behavioural-neurobiological concordance in the effects of cms. *Neuropsychobiology*, 52(2):90–110.
- Wittchen, H.-U., Beesdo, K., Bittner, A., and Goodwin, R. D. (2003). Depressive episodes—evidence for a causal role of primary anxiety disorders? *Eur Psychiatry*, 18(8):384–393.