Selected references – Mats Fredrikson

Agren, T., Engman, J., Frick, A., Bjorkstrand, J., Larsson, E. M., Furmark, T. et al. (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science, 337,* 1550-1552.
Notes: Memories become labile when recalled. In humans and rodents alike, reactivated fear memories can be attenuated by disrupting reconsolidation with extinction training. Using functional brain imaging, we found that, after a conditioned fear memory was formed, reactivation and reconsolidation left a memory trace in the basolateral amygdala that predicted subsequent fear expression and was tightly coupled to activity in the fear circuit of the brain. In contrast, reactivation followed by disrupted reconsolidation suppressed fear, abolished the memory trace, and attenuated fear-circuit connectivity. Thus, as previously demonstrated in rodents, fear memory suppression resulting from behavioral disruption of reconsolidation is amygdala-dependent also in humans, which supports an evolutionarily conserved memory-update mechanism
Department of Psychology, Uppsala University, SE-751 42 Uppsala, Sweden. thomas.agren@psyk.uu.se

Faria, V., Appel, L., Ahs, F., Linnman, C., Pissiota, A., Frans, O. et al. (2012). Amygdala Subregions Tied to SSRI and Placebo Response in Patients with Social Anxiety Disorder. *Neuropsychopharmacology, 37,* 2222-2232.
Notes: The amygdala is a key structure in the pathophysiology of anxiety disorders, and a putative target for anxiolytic treatments. Selective serotonin reuptake inhibitors (SSRIs) and placebo seem to induce anxiolytic effects by attenuating amygdala responsiveness. However, conflicting amygdala findings have also been reported. Moreover, the neural profile of responders and nonresponders is insufficiently characterized and it remains unknown whether SSRIs and placebo engage common or distinct amygdala subregions or different modulatory cortical areas. We examined similarities and differences in the neural response to SSRIs and placebo in patients with social anxiety disorder (SAD). Positron emission tomography (PET) with oxygen-15-labeled water was used to assess regional cerebral blood flow (rCBF) in 72 patients with SAD during an anxiogenic public speaking task, before and after 6-8 weeks of treatment under double-blind conditions. Response rate was determined by the Clinical Global Impression-Improvement scale. Conjunction analysis revealed a common rCBF-attenuation from pre- to post-treatment in responders to SSRIs and placebo in the left basomedial/basolateral and right ventrolateral amygdala. This rCBF pattern correlated with behavioral measures of reduced anxiety and differentiated responders from nonresponders. However, nonanxiolytic treatment effects were also observed in the amygdala. All subgroups, including nonresponders, showed deactivation of the left lateral part of the amygdala. No rCBF differences were found between SSRI responders and placebo responders. This study provides new insights into the brain dynamics underlying anxiety relief by demonstrating common amygdala targets for pharmacologically and psychologically induced anxiety reduction, and by showing that the amygdala is functionally heterogeneous in anxiolysis
Department of Psychology, Uppsala University, Uppsala, Sweden

Thayer, J. F., Ahs, F., Fredrikson, M., Sollers, J. J., III, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart

rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews, 36,* 747-756.
Notes: The intimate connection between the brain and the heart was enunciated by Claude Bernard over 150 years ago. In our neurovisceral integration model we have tried to build on this pioneering work. In the present paper we further elaborate our model and update it with recent results. Specifically, we performed a meta-analysis of recent neuroimaging studies on the relationship between heart rate variability and regional cerebral blood flow. We identified a number of regions, including the amygdala and ventromedial prefrontal cortex, in which significant associations across studies were found. We further propose that the default response to uncertainty is the threat response and may be related to the well known negativity bias. Heart rate variability may provide an index of how strongly 'top-down' appraisals, mediated by cortical-subcortical pathways, shape brainstem activity and autonomic responses in the body. If the default response to uncertainty is the threat response, as we propose here, contextual information represented in 'appraisal' systems may be necessary to overcome this bias during daily life. Thus, HRV may serve as a proxy for 'vertical integration' of the brain mechanisms that guide flexible control over behavior with peripheral physiology, and as such provides an important window into understanding stress and health
Department of Psychology, The Ohio State University, 1835 Neil Avenue, Columbus, OH 43210, USA. Thayer.39@osu.edu

Furmark, T., Henningsson, S., Appel, L., Ahs, F., Linnman, C., Pissiota, A. et al. (2009). Genotype over-diagnosis in amygdala responsiveness: affective processing in social anxiety disorder. *Journal of Psychiatry and Neuroscience, 34,* 30-40.
Notes: BACKGROUND: Although the amygdala is thought to be a crucial brain region for negative affect, neuroimaging studies do not always show enhanced amygdala response to aversive stimuli in patients with anxiety disorders. Serotonin (5-HT)-related genotypes may contribute to interindividual variability in amygdala responsiveness. The short (s) allele of the 5-HT transporter linked polymorphic region (5-HTTLPR) and the T variant of the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene have previously been associated with amygdala hyperresponsivity to negative faces in healthy controls. We investigated the influence of these polymorphisms on amygdala responsiveness to angry faces in patients with social anxiety disorder (SAD) compared with healthy controls. METHODS: We used positron emission tomography with oxygen 15-labelled water to assess regional cerebral blood flow in 34 patients with SAD and 18 controls who viewed photographs of angry and neutral faces presented in counterbalanced order. We genotyped all participants with respect to the 5-HTTLPR and TPH2 polymorphisms. RESULTS: Patients with SAD and controls had increased left amygdala activation in response to angry compared with neutral faces. Genotype but not diagnosis explained a significant portion of the variance in amygdala responsiveness, the response being more pronounced in carriers of s and/or T alleles. LIMITATIONS: Our analyses were limited owing to the small sample and the fact that we were unable to match participants on genotype before enrollment. In addition, other imaging techniques not used in our study may have revealed additional effects of emotional stimuli. CONCLUSION: Amygdala responsiveness to angry faces was more strongly related to serotonergic polymorphisms than to diagnosis of SAD. Emotion activation studies comparing amygdala excitability in patient and control groups could benefit from taking

variation in 5-HT-related genes into account
Department of Psychology, Uppsala University, Uppsala, Sweden.
tomas.furmark@psyk.uu.se

Faria, V., Fredrikson, M., & Furmark, T. (2008). Imaging the placebo response: a neurofunctional review. *European Neuropsycholpharmacology, 18,* 473-485.
Notes: An emerging literature has started to document the neuronal changes associated with the placebo phenomenon. This has altered placebo from being considered a nuisance factor in clinical research to a target of scientific investigation per se. This paper reviews the neuroimaging literature on the placebo effect, and illustrates how imaging tools can improve current understanding of brain mechanisms underlying the placebo response. Imaging studies provide evidence of specific, predictable and replicable patterns of neural changes associated with placebo administration. In general, placebo responses seem mediated by "top-down" processes dependent on frontal cortical areas that generate and maintain cognitive expectancies. Dopaminergic reward pathways may underlie these expectancies. Placebo-induced clinical benefits also involve disorder-specific neuronal responses, yielding neurofunctional or neurochemical alterations similar to those produced by pharmacological treatments
Department of Psychology, Uppsala University, Uppsala, Sweden.
vanda.faria@psyk.uu.se

Fredrikson, M. & Furmark, T. (2003). Amygdaloid regional cerebral blood flow and subjective fear during symptom provocation in anxiety disorders. *Annals of the New York Academy of Sciences, 985,* 341-347.
Notes: Department of Psychology, Uppsala University, Uppsala, Sweden.
Mats.Frederikson@psyk.uu.se
Whether the amygdala is involved predominantly in emotional perception or in the generation of emotional states has been debated. We reviewed and reanalyzed data from our laboratory, indicating that subjective feelings of fear and distress are correlated with regional cerebral blood flow (rCBF) in the right but not the left amygdala during anxiety provocation in individuals with social anxiety disorder, specific phobias. and posttraumatic stress disorder. Positron emission tomography is a correlative technique, and casual inferences cannot be drawn. However, because studies demonstrate that treatment of social anxiety disorder with cognitive behavior therapy and selective serotonin reuptake inhibitors results in reduced rCBF in the amygdaloid complex and prospective studies reveal that treatment-induced alterations in amygdala rCBF can predict 1 year follow-up status in social anxiety disorder data support the notion that the amygdala, at least in part, seem casually involved in generating the subjective experience of fear