

My research program focuses on the neuroscience of anxiety disorders. Although significant progress has been made in the understanding of the neurobiological mechanisms involved in fear conditioning, there remain significant shortcomings in current understanding of anxiety pathology, its etiology, and how to best treat it. My research career thus far has been geared towards addressing this problem, with continuous NIH funding since the start of my position as a UW faculty member in May 2003.

Building on my graduate work using EEG and postdoctoral work using EMG startle, the 6 years of my probationary period have primarily centered on the investigation of anticipatory processing in anxiety disorders using fMRI. The theoretical premise of this line of research is that the anticipation of negative events is a key component of anxiety pathology. The anxiety disorder patients in my clinical practice taught me that such anticipation of potential adverse life circumstances was perhaps the single most debilitating aspect of their pathology. In patients with generalized anxiety disorder (GAD) where extreme worry is the cardinal feature, it is precisely the anticipation of negative events that leads to dysfunction, despite the fact that over 90% of the worries in these patients never come to pass (Borkovec et al., 1999). In social anxiety disorder (SAD), significant social and occupational dysfunction results from anticipating negative social situations. Patients with this disorder anticipate that social activities will result in evaluation, embarrassment, or humiliation. In extreme cases, such patients are unable to go to work or school, or even to leave the home. In panic disorder, it is the anticipation of potentially having an unexpected panic attack that can lead to the same deleterious impact on social and occupational functioning. Similar debilitating consequences of this anticipation of exposure to feared stimuli are also observed for the other two primary anxiety disorders, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD).

To test this hypothesis that the anticipation of aversive events plays a major role in anxiety disorders, we first identified the neural circuitry activated by the anticipation of aversion in healthy volunteers (Nitschke et al., 2006b). We found that the anticipation of aversion recruits the same regions as exposure to aversion, including the amygdala, hippocampus, insula, anterior cingulate, and multiple prefrontal areas. Using different versions of the anticipation task we developed, we have now replicated the findings in multiple additional healthy samples using a variety of emotional stimuli, including pictures, video clips, and tastes (Mackiewicz et al., 2006; Nitschke et al., 2006a, 2009; Oathes et al., submitted; Kerr et al., in prep.). In the course of this work, we also demonstrated that experimental manipulations of expectancy alter brain and behavioral responses to aversion. In a taste study, we found that a misleading cue indicating that a taste would only be mildly aversive resulted in smaller insula responses to a highly aversive taste and less unpleasant perceptions of them (Nitschke et al., 2006a; Sarinopoulos et al., 2006). We also have manipulated uncertainty, a central feature of anxiety, and have shown that uncertain cues (which subjects are told might precede either aversive or neutral pictures) amplified insula and amygdala responses to aversive pictures (Sarinopoulos et al., 2009).

The primary focus of my lab's research efforts then turned to the investigation of how anticipatory brain function on this task is altered in anxiety disorders, including GAD, specific phobia, SAD, and PTSD. We recently reported that GAD patients showed greater amygdala activity in anticipation of emotional pictures than healthy controls (Nitschke et al., 2009). In addition, we found that greater anticipatory anterior cingulate activity was associated with better clinical outcome following 8 weeks of treatment (Nitschke et al., 2009). In an independent sample of GAD patients for whom we also collected DNA samples, we found that the pattern of heightened anticipatory amygdala activity was primarily driven by individuals with 5-HTTLPR and rs25531 indicators of increased serotonin transporter expression (Oathes et al., submitted). These findings are consistent with a recent report in adolescents with affective disorders (Lau et al., 2009) and add to the new literature on the interface of serotonin gene variants and brain function in anxiety and depression pathology. We also conducted diffusion tensor imaging in this second sample of GAD patients and found that they had drastically reduced structural connectivity compared to healthy controls in the uncinate fasciculus, which is the key white matter tract connecting the amygdala to ventral prefrontal and anterior cingulate regions (Tromp et al., in prep.). These structural data suggest a possible mechanism for limited down-regulation of the anticipatory

amygdala activity by prefrontal and anterior cingulate areas in GAD. Finally, we have also completed data collection for a study on specific phobia and found that snake phobics showed greater anticipatory activity than nonphobic, healthy controls in the insula, amygdala, and anterior cingulate in response to a cue that preceded 3-s video clips of snakes, but not in response to cues that preceded disgusting or neutral video clips (Kerr et al., in prep.). These latter two studies already have complete drafts that are being revised for manuscript submission to *Archives of General Psychiatry* and *American Journal of Psychiatry*, respectively (both studies were presented at major scientific meetings since June 2009 – see (f) Conference Proceedings below).

Goals for future

In the near future, we will be pursuing new directions on several different fronts. First, we will investigate whether the anticipatory abnormalities identified for GAD and specific phobia are also present in other anxiety and mood disorders. A neuroimaging study of SAD and major depressive disorder (as well as GAD) in our lab is nearing completion. Because comorbidity among the anxiety and mood disorders is the rule rather than the exception (and a longstanding interest of mine dating back to my graduate work), that study also enrolls subjects who meet diagnostic criteria for two or more of those disorders in order to assess the impact of comorbidity on anticipatory brain activity. In collaboration with Drs. Eileen Ahearn and Tracey Smith at the Madison VA, we recently embarked on a large neuroimaging study of PTSD in soldiers returning from the Iraq and Afghanistan conflicts that uses an anticipation paradigm with thermal pain. This work is currently funded by my Dana and ICTR grants, and I will be submitting my R01 revision for this study in July 2010. Second, I am committed to the continued development and implementation of new techniques for assessing functional and structural connectivity among the nodes of the anticipatory network we have identified. I hired an information processing consultant, Dr. Dan McFarlin, for this express purpose, and our recent and upcoming publications showcase the methodological developments in this area. This work will be featured prominently in my R01 renewal to be submitted in June 2010. Third, neuroimaging genetics is a burgeoning field with significant potential for the study of anxiety disorders. This area will clearly need to move beyond the emphasis on single polymorphisms that currently characterizes the field, which drives my increasing contact with Dr. Josh Hyman and other geneticist colleagues at UW. A new graduate student who joined my lab to conduct neuroimaging genetics research further attests to my strong interest in pursuing this new direction in my lab. Finally, I am committed to using my research to benefit those suffering from anxiety disorders. This may come in part as a result of our research examining anticipatory processing in the pathophysiology of anxiety disorders. I also intend to increasingly employ treatments in our neuroimaging studies of anxiety disorders as a logical next step building on the basic and clinical research conducted in my lab to date. Our initial study on GAD discussed above (Nitschke et al., 2009) included a treatment arm (medication), and the PTSD study we recently began includes two treatment arms (psychotherapy and medication).