Summary and concluding remarks

The initial part of this thesis concerns the 35% CO₂ challenge as an experimental model for panic. A considerable amount of previous work has shown that the challenge is specific, clinically valid and reliable, necessary properties for a good experimental model. Symptom convergence between consecutive challenges was also proven to be good. However, the matter of symptom convergence between experimentally provoked and naturally occurring panic attacks was still open. The study in chapter 2 shows that the 35% CO₂ panic challenge reproduces well the majority of symptoms of real-life panic attacks. This study therefore further establishes the value of the challenge as an experimental model and as a diagnostic test for panic. The test can be used as an aid to differentiate between different anxiety disorders. However, an experienced clinician might not often need such a test to make a diagnostic decision. Matters may be different when a differential diagnosis must be made with somatic complaints with an unclear clinical picture or resembling conditions like, for example, myocardial infarction or irritable bowel disorder. In this field might lie the greatest opportunities for the 35% CO₂ challenge as a diagnostic instrument in daily clinical practice. First steps in this direction have already been made, by the group of Adriaan Honig from our department, in collaboration with our group.

The major part of this thesis, however, is devoted to the study of the neurobiological mechanisms of panic disorder and, more specifically, of the unexpected panic attack which is the core of the disorder. In these studies, the 35% CO₂ challenge is not as much used as a diagnostic test, but as an experimental model for the key element of panic disorder. Other, biochemical manipulations were then used to study different aspects. The combination of challenge methods like in chapter 3, where CO₂ and cholecystokinin (CCK) challenges were combined, proved to be a fruitful way of gaining more insight in the pathophysiology of panic. The results suggest that both challenges act upon different neural mechanisms and raised some important questions that must be answered in future research. These include the effects of simultaneous rather than consecutive administration of two different panicogens, or the administration in reverse order.

In chapter 4, the respiratory effects of CCK were examined. Outcome measures of the experiment were not only subjective reports of anxiety or neurovegetative symptoms, but also
objective measurements of respiratory parameters. It was shown that CCK has direct effects on respiration, possibly important for its panicogenic effect, independent of its effect on anxiety or panic symptoms. Future research in patients should take both these aspects into account.

Chapters 5 to 8 are about the role of serotonin (5HT) in panic. In chapter 5 it is shown that lowering 5HT availability to the brain increases vulnerability to a 35% CO₂ panic challenge. The results from chapter 6 show that there is probably no 5HT receptor hypersensitivity in panic disorder. Chapter 7 is the converse experiment of chapter 5, showing that increasing availability of 5HT reduces the reaction to the challenge. These three chapters together confirm that 5HT indeed has a very important role in panic.

However, contrary to what is proposed by some, this role is probably not a causal but rather a modulatory one. This is possibly the most important conclusion from this thesis.

Notwithstanding the important role of 5HT, the results from chapter 8 show that the mechanism of 5HT reuptake, by which most of the effective medications for PD are thought to act, is not crucial for the effect of pharmacological treatment of PD. The results also point out that focusing on one particular neurotransmitter system, for research purposes, bears the danger of forgetting other neurotransmitter systems that are of importance. An example is the noradrenergic system, which seems to have become "out of fashion". Very much in fashion, on the other hand, is the hypothalamus-pituitary-adrenal axis, and especially corticotropin releasing hormone which not only has a neuroendocrine role but also acts as a neurotransmitter. Finally, recent research also implicates immunological factors in the pathophysiology of panic disorder. Cytokines have been shown to influence 5HT metabolism and have a reciprocal influence on different elements of the HPA-axis. Ongoing and future research at the Academic Anxiety Center will include neuroendocrine aspects of panic disorder as well as other anxiety disorders. Joint ventures including immunological expertise may prove fruitful as well.

Other synergies may be interesting as well. The effect of biochemical substances and the production of neurotransmitters is often confined to discrete regions in the brain.

For example, the panicogenic effect of CO₂ probably involves activation of brain centers such
as the chemoreceptor trigger zone, nucleus tractus solitarius and periaqueductal gray. CCK is also supposed to act upon the nucleus solitarius. Additionally, most of the serotonergic neurons in the brain originate from the raphe nuclei. However, the experimental models we have used up to now only provide indirect evidence as to the neurocircuitry involved in panic. Therefore, a topographical approach such as that provided by modern neuroimaging techniques may ideally complement the approach used in experimental psychiatry. Of the different techniques available, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) seem the most promising. These techniques also offer the advantage that they provide information which is independent of the subjective reports of study participants.

Several problems remain to be solved, however. Spatial resolution of PET is insufficient to visualize some of the small brain stem centers that are involved in panic. The technique can deliver more precise information by using radioactive ligands for specific receptors. However, their availability is still limited. fMRI has a much higher spatial resolution but shows other drawbacks. For example, making an MRI scan involves lying in the narrow tunnel of the scanner for quite some time. This is an extremely difficult task for patients with panic disorder, who are typically afraid of places where escape is difficult in the event of a panic attack. These difficulties probably explain why, up to now, only very few functional imaging studies have been performed in panic disorder. Nevertheless, neuroimaging techniques, as well as neuroendocrine and immunological studies offer exciting possibilities to learn more about the pathophysiology of panic disorder.