Summary

Tuberous sclerosis complex (TSC) is a multisystem genetic disease caused by mutations in the *TSC1* and *TSC2* genes, encoding for the proteins hamartin and tuberin. These proteins form a complex that acts as a negative regulator of mechanistic target of rapamycin complex 1 (mTORC1), a major hub integrating multiple intra- and extracellular signaling pathways. Neurological manifestations of TSC include epilepsy, benign tumors, and TSC-associated neuropsychiatric disorders (TANDs). TAND is a broad classification that include various cognitive, behavioral and mood disorders, including, among others, anxiety and autism spectrum disorder (ASD). The precise etiology of the various conditions and symptoms that occur in TSC patients has not yet been fully elucidated. The aim of this thesis, following previous findings obtained by our group, was to uncover the mechanisms underlying selected aberrant behaviors observed in the zebrafish model of TSC, the *tsc2*^{vu242} mutant. Chapter 1 provides general background information on TSC and TANDs. The next part of this work, comprised of chapters 3-4, introduces the zebrafish as a useful model for epilepsy research, and presents state-of-the-art methodology for studying zebrafish brain activity and behavior. In chapter 5, I uncovered the mechanism by which mTorC1-hyperactive neurons in the left dorsal habenula (LdHb) result in an aberrant response to light. Through a calcium imaging experiment, I found that LdHb neurons in the *tsc2*$^{vu242/vu242}$ mutant do not properly integrate light stimuli, and show impaired habituation to light. As a consequence, the mutant larvae display lowered light preference in comparison to wild-type siblings. I have also confirmed that pretreatment with the mTorC1 inhibitor rapamycin rescues the dysregulation of both neuronal activity and behavior. These findings are of potential relevance to patients with ASD, who frequently experience hypersensitivity to sensory stimuli. Additionally, chapters 6-7 include two protocols used in that study, for whole-mount immunofluorescence and microinjections of rapamycin into the zebrafish brain In chapter 8, I explored the role of TrkB pathway in anxiety, and the patterns of neuronal activity across various telencephalic territories related to fear and anxiety. I have confirmed that the *tsc2*$^{vu242/vu242}$ fish display anxiety-like behaviors, which are rescued by treatment with the TrkB inhibitor ANA-12. I have also found regions of hypo- and hyperactivated neuronal activity in the habenulae, pallium and subpallium of *tsc2*$^{vu242/vu242}$ fish, many of which were regulated by ANA-12. This suggests that the TrkB pathway plays an extensive role in the anxiety circuitry of the zebrafish brain. Based on the location of affected regions and the expression of marker proteins, I have putatively identified them as parts of the amygdaloid complex. Up to date, a comprehensive comparative analysis between the mammalian and zebrafish amygdala has only been conducted on adult zebrafish. Therefore, mapping the amygdaloid territories in the developing zebrafish brain provides a novel insight into the earliest root causes of anxiety disorders. Lastly, chapter 8 discusses the conclusions and potential future directions for studies into selected TSC-associated disorders. Taken together, the findings of this thesis shed light on previously undescribed molecular mechanisms contributing to TANDs, and form a basis for future research into the etiology of ASD and anxiety in TSC.