Understanding the emotional brain

Most of the modern brain research focuses on sensory and cognitive functions, since these processes can be studied objectively in the laboratory and modelled as computer-like operations. However, a purely cognitive approach is an unrealistic view of the brain. Brains are not only information-processing devices but also possess goals, strivings, hopes, desires and fears. Emotional expression is a fundamental aspect of behaviour and, as Darwin already noticed in 1872, it is present across species and cultures. Cognitive and emotional processes are intermingled and it is well known, for example, that stress affects cognition and learning. Thus, to truly understand the brain we must understand both cognitive and emotional processes.

This research aims to define the role of anatomically-identified neurons in shaping the functional properties of neuronal circuits of the brain region known as amygdala.

The first challenge in this kind of research is to find a model to study labile and subjective emotions in the laboratory. Neuroscientists study emotions experimentally by using a behavioural paradigm called fear conditioning. In this way, ‘fear’ is studied as a set of processing circuits that detect and respond to ‘dangerous’ stimuli, rather than as a purely cognitive approach is an unrealistic view of the brain. Brains are not only computer-like operations. However, a purely cognitive approach is an unrealistic view of the brain. Brains are not only information-processing devices but also possess goals, strivings, hopes, desires and fears. Emotional expression is a fundamental aspect of behaviour and, as Darwin already noticed in 1872, it is present across species and cultures. Cognitive and emotional processes are intermingled and it is well known, for example, that stress affects cognition and learning. Thus, to truly understand the brain we must understand both cognitive and emotional processes.

Suppressing fear
Fortunately fear conditioning can be reduced or suppressed. Such fear extinction is progressively achieved by exposing an animal to the CS in the absence of the US. This process is likely to be an active form of learning that counteracts but does not simply erase the acquired fear response. The extinction is a highly translational phenomenon since it is the corner-stone of many psychological therapy of anxiety in humans. So which brain circuits underlie fear conditioning? Converging evidence from many laboratories suggests that the amygdala, a brain structure located in the temporal lobe, is crucially involved. The amygdala is well placed in the brain to perform this task because it receives highly processed information from all sensory modalities and projects broadly to other brain areas involved in the autonomic and somatic aspects of fear and anxiety. The amygdala is a necessary but not a sufficient neural substrate of extinction since other brain regions such as the medial prefrontal cortex (mPFC) and the hippocampus have also been shown to be crucial components of the brain’s extinction circuitry. Remarkably, data from animal and human studies converge: a similar pattern of activation of mPFC and inhibition of the amygdala is seen in rodents and humans during the recall of fear extinction. There is some agreement amongst neuroscientists that extinction develops when pathways conveying sensory information to the amygdala engage cells releasing the inhibitory transmitter GABA through some form of experience-dependent plasticity. Recent studies in rodents have extended this idea to implicate specific circuits. The amygdala contains islands of GABAergic interneurons, known as intercalated cells (ITCs) that are suggested to inhibit the central nucleus output neurons of the amygdala. Stimulation of the mPFC increases immediate-early gene expression in ITCs, reduces the excitability of central output neurons, and depresses fear conditioned immobility. Thus, the mPFC could gate fear expression and underlie fear extinction through a powerful ‘off-switch mechanism’ within the amygdala, mediated by the ITCs. From a clinical point of view, this would be desirable to selectively activate ITCs, but this may prove to be difficult.

Defining the ITC network
A major problem to prove this idea is that little is known about ITCs of the amygdala. Therefore, we have initiated a research programme to define the ITC network, their inputs and outputs, and test experimentally their involvement in fear extinction in vivo. We use a transgenic mouse line expressing the green fluorescent protein (GFP) under the control of the GAD65 promoter. Since GAD65 is an enzyme used by the cells to synthesise GABA, GFP-positive neurons observed by immunofluorescence in slices obtained from this transgenic mouse must be GABAergic cells. Therefore, the use of this mouse line facilitates the identification of green fluorescent GABAergic ITCs. By using this transgenic mouse, we have recently reported novel insights into the synaptic organisation of the ITCs of amygdala. Whole-patch clamp recordings have been performed from visually-identified GFP positive ITCs. Surprisingly, we discovered that the neuronal network formed by these neurons is composed by different types of cells. In spite of being all of them aligned with their cell body along a thin strip of tissue within the amygdala, their synaptic coupling changes dramatically amongst different pairs of neurons. Some pairs of ITCs show a remarkably strong synaptic connection but others display an average or even an unusually weak synaptic connectivity. The frequency of activity of the presynaptic ITCs determines whether the connection is strong or weak. Interestingly, these functional differences are also correlated to differences in the morphological aspect of the cells. Theoretical models predict that synapses with heterogenous synaptic strengths can contribute to maintaining stability of activity in the cellular network. Our can speculate that the diverse functional connectivity of ITCs is required to maintain the stability of cell activity and this is critical for the computational role of the amygdala in fear extinction.

In the future we plan to study the firing patterns of ITCs of amygdala in vivo. We will investigate whether the firing patterns tend to stabilise in different brain states, as suggested by our work in vitro. Our long-term aim is to assign specific roles to ITCs in fear extinction in order to advance the neural basis of fear as an important area of research in neuroscience.

The Amygdala Interneuron project aims to determine the firing pattern of ITC neurons. This will represent an important milestone in neuroscience, says Dr. Marco Capogna, who expands on the key role his initiative is playing in advancing research.