Research Briefings

# Thomas Theil
# Patterning and axon pathfinding in the forebrain

**THE CEREBRAL CORTEX IS RESPONSIBLE FOR ALL HIGHER COGNITIVE FUNCTIONS UNIQUE TO HUMANS AND CONTAINS AN ENORMOUS VARIETY OF NEURONS. HOW IS THIS VARIETY GENERATED DURING DEVELOPMENT? HOW ARE THESE NEURONS CONNECTED? TO ADDRESS THESE QUESTIONS WE USE THE MOUSE AS A MODEL. WE INVESTIGATE THE FUNCTION OF TRANSCRIPTION FACTORS AND SIGNALLING SYSTEMS REQUIRED FOR THE CORRECT FORMATION OF THE CORTEX.**

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## INTRODUCTION

The cerebral cortex is responsible for all higher mental and cognitive functions unique to humans. Disruption of its function underlies a variety of different neurological disorders such as certain forms of epilepsy and mental retardation. To fulfil its role the cortex requires an enormous variety of different neurons, far more than in any other part of the brain. This striking degree of neuronal diversity is generated during embryonic development. Furthermore, cortical neurons have to make appropriate axonal contacts with neurons either within or outside the cortex to allow the establishment of a functional cortical circuitry. The general aim of our research is to better understand the mechanisms which lead to the generation of these different types of cortical neurons and how the axonal connections between these neurons are established.

To address these questions, we are using the mouse as a model organism and we are particularly interested in the role of the *Gli3* zinc finger transcription factor. The human GLI3 gene is mutated in a number of syndromes, including the Acrocallosal Syndrome (ACS) and Greig cephalopolydactyly Syndrome (GCPS). Such patients may suffer from mental retardation due to the absence of the corpus callosum, the major fiber tract connecting the two cerebral hemispheres. In our lab, we are characterizing cortical development in Gli3 mutant mice to identify the mechanisms which lead to mental retardation in GLI3 syndrome patients.

## PATTERNING THE TELENCEPHON

The cerebral cortex develops from the

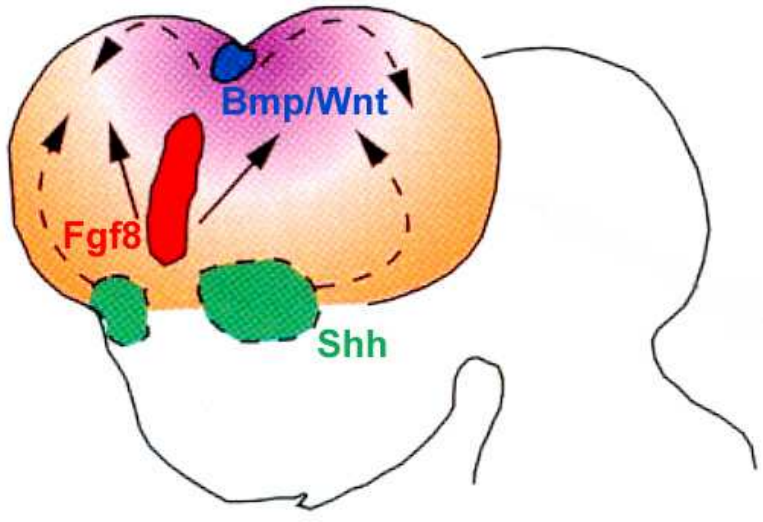


**Fig. 1**: Patterning of the telencephalon is controlled by three signalling centers.

dorsal telencephalon. In an early phase of its development, the telencephalon becomes subdivided into different regions including the cortex. This regionalization process is governed by a number of signalling molecules. These are produced locally and form concentration gradients, thereby controlling the development of adjacent telencephalic cells. For example, the expression of Wnt genes in the dorsal midline of the telencephalon, the cortical hem, is required for the development of the hippocampus, an important cortical structure which is involved in memory and learning. In the Gli3 null mutant extra-toes ($Xt^J$), the cortical hem fails to form and these Wnt genes are not expressed leading to the absence of the hippocampus. We are currently using a microarray screen comparing the expression patterns of genes in the wildtype and $Xt^J/Xt^J$ telencephalon to identify genes which are regulated by Wnt genes in the developing hippocampus.

## FORMATION OF AXON TRACTS IN THE DEVELOPING CORTEX

Once cortical neurons have been specified they have to make proper contact with their target cells. Prominent among these axonal connections of the cerebral cortex are the corpus callosum which connects the two cerebral hemispheres and

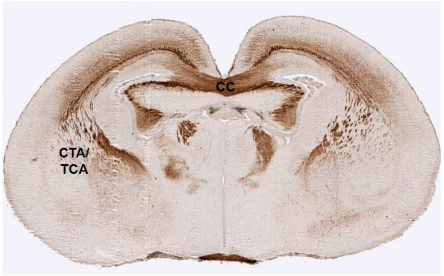


**Fig. 2:** The cerebral cortex makes specific axonal connections which can be revealed by neurofilament staining. The corpus callosum (CC) connects neurons in the two cerebral hemispheres while the thalamocortical (TCA) and corticothalamic (CTA) tract provide connections between the cortex and the thalamus.

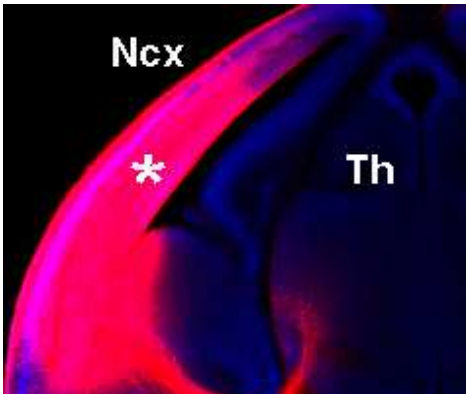


**Fig. 3:** DiI crystal (*) injection into the neocortex (ncx) reveals the corticothalamic tract.

the corticothalamic/thalamic tract which conveys information between the thalamus and the cortex. We are investigating the molecular mechanism which control the formation of these fiber tracts and we are specifically interested how early patterning defects in the telencephalon may lead to axon pathfinding defects in the cortex. To this end, we are using the Polydactyly Nagoya (Pdn) mouse mutant which carries a hypomorphic Gli3 mutation and Gli3 conditional knock-out mice. We could already show that, similar to Acrocallosal patients, Pdn mutants lack the corpus callosum and also have defects in the development of the corticothalamic/thalamocortical tract. Currently, we are investigating how early regionalisation defects present in these mutants can cause these axon pathfinding defects.

**Selected references**

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Research supported by
Deutsche Forschungsgemeinschaft (DFG),
The Wellcome Trust,
Medical Research Council (MRC).